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Globimetula braunii prevents hyperglycemia, oxidative damage, and hepatorenal dysfunction in dexamethasone-induced insulin-resistant rats

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ABSTRACT

Introduction: *Globimetula braunii* is a parasitic plant used in Cameroon in traditional medicine to treat diabetes mellitus. The present work aimed to evaluate the protective effects of aqueous leaf extract of *G. braunii* (EGB) on rats rendered insulin-resistant by dexamethasone.
Methods: To induce insulin resistance, male rats received a subcutaneous dexamethasone injection (1 mg/kg) daily for 10 days. One hour before the administration of dexamethasone, the animals received vehicle, metformin (40 mg/kg), or EGB (120, 240, and 480 mg/kg). Body weight, glycemia, insulinemia, homeostatic model assessment for insulin resistance (HOMA-IR), markers of kidney and liver functions, and oxidative profile were assessed.
Results: EGB (240 and 480 mg/kg) caused a significant decrease ($P<0.001$) in body weight on day 10, hyperglycemia, insulinemia, insulin resistance, and a notable increase ($P<0.001$) in the transaminases activities, as well as uric acid and creatinine levels. Additionally, EGB at all doses caused a significant increase ($P<0.001$) in reduced glutathione level and glutathione peroxidase activity in the liver and in superoxide dismutase and catalase activities in the kidneys of the rats. Malondialdehyde levels were significantly decreased in the kidneys of EGB-treated animals at doses of 240 and 480 mg/kg. EGB (240 and 480 mg/kg) also reversed kidney and liver damage caused by hyperglycemia.
Conclusion: EGB has remarkable hypoglycemic, hepatoprotective, and nephroprotective properties and protects organs against damage caused by oxidative stress, thus validating the ethnopharmacological use of this plant in the management of diabetes mellitus and some of its comorbidities.

Implication for health policy/practice/research/medical education:
The aqueous extract of *Globimetula braunii* has hypoglycemic potential and protects organs against damage caused by oxidative stress, which is why its use is recommended in traditional medicine for the management of diabetes mellitus.
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Introduction

Diabetes mellitus is a protein, carbohydrate, and fat metabolic disorder characterized by chronic hyperglycemia. It is due to insufficient action (type 2 diabetes) and/or insufficient insulin production (type 1 diabetes) (1). Urbanization, lifestyle changes, sedentary lifestyles, obesity, and psychosocial stress constitute the main risk factors for the development of the disease. Diabetes can lead to complications such as myocardial infarction, stroke, kidney failure, limb amputation, vision loss, and nerve damage. Hyperglycemia is also associated with an overproduction of free radicals,

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thereby contributing to the angiopathic complications of diabetes (2). Diabetes is causing more and more victims across the world. Worldwide, there are approximately 537 million people aged 20 to 79 with diabetes, representing a prevalence of 10.5%. An increase of approximately 643 million by 2030 and 784 million by 2045 is predicted (3). In 2021 alone, there were nearly 6.7 million deaths caused by diabetes worldwide (3).

The management of diabetes requires drug treatments associated with good dietary hygiene. It is very expensive in a hospital setting and requires the combination of several therapies. Insulin is the main medication for type 1 diabetes while lifestyle and diet changes form the basis of treatment for type 2 diabetes (4). Today, low-income populations do not have access to prohibitively expensive synthetic antidiabetic drugs. These reasons direct diabetic patients towards herbal medicine. There are more than 400 plants in nature that have antidiabetic properties (5). The World Health Organization (WHO) recommends medicinal plants, individually or in combination, for diabetes management and its complications (6). The bioactive compounds identified and isolated from these plants make it possible to elucidate their mechanisms of action.

Globimetula braunii Engl. Danser, known as 'Gui d'Afrique' in French and 'Kauchii' in Hausa, is a parasitic plant (Lauranthaceae) traditionally used to treat diabetes, wounds, high blood pressure, heart problems, anxiety, insomnia, headaches, leg pain, lung disorders, ulcers, and cancer (7). It is a species from tropical regions widely distributed in Ghana, Cameroon, and Nigeria. Its branches are pendulous or erect, and its leaves are pink or red, oval with a rounded base, thick, and variable size (8). A previous study has shown the hypoglycaemic property of leaf extract of *G. braunii* in alloxanized diabetic albino rats (9). Furthermore, its antioxidant potential has been proven on methanol and ethyl acetate leaf extracts of *G. braunii* (10). Phytochemistry on *G. braunii* revealed the presence of flavonoids, steroids, triterpenes, tannins, alkaloids, and saponins (11). In addition, further studies made it possible to isolate several compounds, including seven flavonoids (rutin, quercetin, rhamnetin, catechin, quercitrin, rhamnetin-3-O-α-L-rhamnopyranoside, and avicularin) in leaf extract of *Globimetula braunii* and several other compounds (12-14). However, *G. braunii* has not yet been tested in an insulin-resistant animal model. Therefore, the present work aimed to evaluate the protective effects of aqueous leaf extract of *G. braunii* on rats rendered insulin-resistant by dexamethasone.

Materials and Methods

Harvesting and identification of plant material

Globimetula braunii leaves (a guaranteed parasite) were collected in September 2021 in Meiganga (Cameroon), located between 6°31'0" and 5°38' North latitude and between 10°02' and 10°08' East longitude. The species collected was authenticated at the National Herbarium of Yaoundé (Cameroon) and registered under the number 24663/SRF/Cam. The leaves of *G. braunii* were cut, washed, and dried in open-air and shade for 15 days. Then, they were ground using a mill until a powder was obtained.

Aqueous extraction of *Globimetula braunii* leaves

Three hundred grams (300 g) of *G. braunii* leaf powder was poured into 1000 mL of hot distilled water. Everything was left in a closed pot for 40 minutes and filtered with Whatman No. 1 paper. The liquid obtained (filtrate) was evaporated in an oven at 45 °C to obtain the crude extract (mass 36 g; yield 12%).

Determination of EGB doses

The doses of EGB used were determined based on information collected from traditional practitioners. The daily dose for a patient is two glasses, obtained by introducing two tablespoons of *G. braunii* powder (14.7 g) into two glasses of previously boiled distilled water (500 mL). The potion prepared by the traditional practitioner was filtered and placed at 45 °C in an oven for 48 hours to evaporate. This mass of extract administered to an adult weighing 70 kg made it possible to obtain the human therapeutic dose (HTD): HTD = 2.8 g/70 kg = 40 mg/kg. The formula of Shannon et al (15) made it possible to calculate the rat equivalent dose (EDR): EDR = HTD × human Km/rat Km, where human Km = 37, rat Km = 6, Km = specific conversion factor. This EDR obtained (240 mg/kg) was supervised by two other doses (120 and 480 mg/kg). Therefore, the doses of EGB used in this study were 120, 240, and 480 mg/kg.

Animals

Male rats of the Wistar strain, aged 10 to 12 weeks and weighing 180 to 200 g, were used. They were provided by the animal facility of ENSAI (National School of Agro-industrial Sciences) of the University of Ngaoundéré (Cameroon). Rats kept in polystyrene cages underwent 2 weeks of acclimation to laboratory conditions (relative humidity, room temperature, and 12 h/12 h light/dark cycle). They received unlimited drinking water and a standard diet daily. The protocols used for the experiments were conducted in accordance with internationally recognized principles for the use of laboratory animals approved by the National Ethics Committee of Cameroon (Ref. No. FWIRB 00001954).

Distribution of animals and insulin resistance induction protocol

The insulin resistance induction protocol with dexamethasone (Dexa) was described by Njan et al (16). Indeed, 30 animals were distributed in six groups (n = 5) and received, for 10 days, the various treatments. Rats in the 1st group (normal control) received distilled water

(10 mL/kg p.o.) + 0.9% NaCl (1 mL/kg i.m.); rats in the 2nd group (diabetic control) received distilled water (10 mL/kg po) + Dexa (1 mg/kg i.m.); rats in the 3rd group (standard control) received metformin (40 mg/kg p.o.) + Dexa (1 mg/kg i.m.); rats in groups 4, 5, and 6 received EGB at respective doses of 120, 240, and 480 mg/kg p.o + Dexa (1 mg/kg i.m.) each. Intramuscular treatments were administered one hour after the oral pretreatment. The body mass of the animals was checked on days 0, 5, and 10 of treatment (16).

Blood and organ samples

After a 24-hour fast, the animals were anesthetized by intraperitoneal administration of a diazepam/ketamine combination (Bexwell, UK) (20 mg/kg/10 mg/kg) and then sacrificed by cervical decapitation. The blood was collected from the jugular vein, introduced into dry tubes, and then centrifuged (Beckman Coulter J26-XPI centrifuge, USA) at 3000 rpm for 5 minutes. The supernatant was collected and preserved for the different assays. Additionally, kidneys, pancreas, and liver were collected and then cleaned in NaCl 0.9% (Bexwell, UK). A part of the liver or kidneys was ground in a mortar to prepare the organ homogenate (15 g of organ in 85 mL of 0.02 M Tris buffer, pH 7.4). The supernatant, obtained after centrifugation at 4900 rpm for 20 minutes, was collected and stored at -20 °C for subsequent assays of oxidative stress parameters. The pancreas and other parts of the liver and kidneys were preserved in 10% formalin for histopathological studies.

Blood sugar, insulinemia, HOMA-IR, and HOMA-β

The animals' fasting serum glucose levels were determined with a One Touch Ultra Mini brand glucometer (Life Scan, USA). The serum insulin level was assessed using a rat ELISA (enzyme-linked immunosorbent assay kit) (Sigma-Aldrich, USA) (17). Insulin resistance was assessed using the homeostatic model assessment for insulin resistance (HOMA-IR): HOMA-IR = (fasting insulin × fasting blood glucose)/22.5 (18). Pancreatic β-cell function was determined using the β-cell Function Assessment Model (HOMA-β): HOMA-β = 20 × (fasting insulin) / (fasting blood glucose -3.5) (19). The insulin sensitivity index (ISI) was determined as follows:

ISI = 1 / (log [fasting insulin] + log [fasting blood glucose]) (18).

Evaluation of markers of hepatorenal function

The activities of aspartate aminotransferase (AST), alkaline phosphatase (ALP), and alanine aminotransferase (ALT) were evaluated following the experimental method described by Reitman and Frankel (20). The Biuret method was used to determine the serum total protein level (21). Total and conjugated bilirubin levels were measured following the protocol of Maity et al (22). Albumin, creatinine, uric acid, and urea levels were measured using assay kits (Sigma-Aldrich, USA).

Evaluation of oxidative stress parameters

The oxidative profile was carried out on non-enzymatic and enzymatic antioxidants in animals' kidneys and livers using commercial kits (Sigma-Aldrich, USA). The activities of catalase (CAT), superoxide dismutase (SOD), and glutathione peroxidase (GPx) were evaluated by the respective methods of Begg and Woods (23), McCord and Fridovich (24), and Burk et al (25). The protocols described by Polizio and Pena (26) and Bump et al (27) were those used to quantify malondialdehyde (MDA) and reduced glutathione (GSH) levels, respectively.

Histological examination

Renal and liver tissue sections were made using the method of Bancroft and Gamble (28). After fixing the organ fragment in formalin, it was cut into pieces and passed successively through baths of alcohol of increasing concentration, toluene, and paraffin for dehydration and inclusion. Then, the tissue blocks were placed in the freezer for hardening, fixed on the microtome (Thermo Electron Corporation, England), and cut (5 µm). The cut tissues were stained with hematoxylin and eosin, mounted on the slides using Canada balsam, and observed under an Olympus brand microscope (X400). Photomicrographs were taken using an Olympus camera mounted on the microscope.

Statistical analysis

Data were presented as mean ± SEM (standard error of the mean). GraphPad Prism software version 8.01 was used to analyze the data. Data between different groups were compared using a one-way analysis of variance (ANOVA) followed by Turkey's post-test. Differences were considered significant at $P<0.05$.

Results

Effects of EGB on relative body mass

Dexamethasone induced a notable decrease ($P<0.001$) in the relative body mass of rats throughout the treatment period. However, administration of EGB (240 and 480 mg/kg) and metformin reduced the action of dexamethasone leading to an increase in body mass on the 5th ($P<0.01$) and 10th ($P<0.001$) days of the experiment (Figure 1).

Effects of EGB on glycemia, insulinemia, insulin resistance, and insulin sensitivity

Dexamethasone caused a significant increase ($P<0.001$) in the HOMA-IR value and glucose and insulin levels, and a notable decrease ($P<0.001$) in the ISI value (Table 1). On the other hand, the administration of EGB and metformin resulted in effects opposite to those of dexamethasone, namely a significant reduction ($P<0.001$) in blood glucose, insulinemia, and HOMA-IR values, and a significant increase ($P<0.01$ to $P<0.001$) in the ISI value.

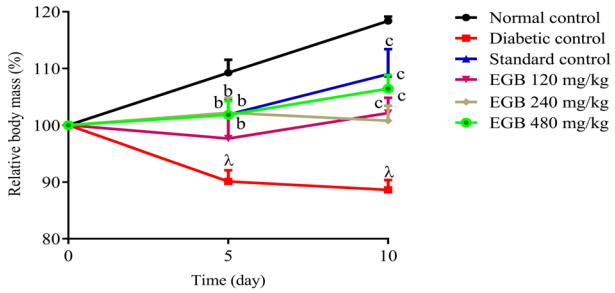

Figure 1. Effects of *Globimetula braunii* leaf extract (EGB) on the relative body mass of insulin-resistant animals. Data are presented in mean ± SEM (n = 5). λ: $P < 0.001$ compared with normal control; c: $P < 0.001$ and b: $P < 0.01$ compared with diabetic control.

The HOMA-β index values in different groups of animals did not vary significantly (Table 1).

Effects of EGB on biomarkers of hepatorenal function

There was a notable increase ($P<0.001$) in the levels of creatinine and uric and the activities of ALT, AST, and ALP, accompanied by a decrease ($P<0.05$) in serum TP concentration in untreated insulin-resistant animals (Table 2). In contrast, the standard and EGB at all doses resulted in a reduction ($P<0.05$; $P<0.001$) in transaminase activities and levels of TB, CB, creatinine, and uric acid, as well as an increase ($P<0.05$) in the concentration of TP in the serum of rats. Urea levels did not significantly change after EGB administration (Table 2).

Effects of EGB on oxidative profile

There was a significant decrease ($P<0.001$) in the activities of antioxidant enzymes such as CAT, GPx, and SOD in animals in the diabetic control group compared to the normal control group. GSH levels were also decreased in the liver ($P<0.05$) and kidney ($P<0.01$) of these animals. In contrast, there was a significant increase in MDA levels in the liver ($P<0.05$) and kidney ($P<0.01$) of animals in the diabetic control group. Compared to the diabetic control, a significant decrease in the MDA levels was noted in the liver of animals treated with the standard ($P<0.001$) and EGB at doses of 120 ($P<0.01$), 240 ($P<0.01$) and 480 mg/kg ($P<0.001$), and in the kidneys of rats having received the standard ($P<0.001$) and EGB at doses 120 ($P<0.05$), 240 ($P<0.01$) and 480 mg/kg ($P<0.01$). In contrast, the administration of different doses of EGB and metformin resulted in a significant increase in GSH levels in the liver ($P<0.001$) and kidney ($P<0.05$) of insulin-resistant animals. Similarly, there was an increase in CAT activity in the liver of animals treated with metformin ($P<0.01$) and EGB at 120 ($P<0.01$), 240 ($P<0.01$), and 480 mg/kg ($P<0.001$), and in the kidneys ($P<0.001$) of rats receiving

Table 1. Effects of *Globimetula braunii* leaf extract (EGB) on glycemia, insulinemia, HOMA-IR, ISI, and HOMA-β in insulin-resistant animals

Groups	Glycaemia (mg/dL)	Insulinemia (U/mL)	HOMA-IR	ISI	HOMA-β
Normal control	71.50 ± 7.42	48.51 ± 2.79	154.15 ± 14.23	1.85 ± 0.25	14.26 ± 0.93
Diabetic control	127.50 ± 9.40$^{\lambda}$	85.21 ± 5.21$^{\lambda}$	482.85 ± 17.66$^{\lambda}$	0.96 ± 0.11$^{\lambda}$	13.74 ± 2.17
Standard control	87.75 ± 5.62^{c}	53.46 ± 3.32^{c}	208.49 ± 21.32^{c}	1.48 ± 0.18^{b}	12.69 ± 0.83
EGB 120 mg/kg	102.25 ± 4.72^{c}	50.18 ± 2.21^{c}	228.04 ± 14.75^{c}	1.41 ± 0.13^{b}	10.16 ± 1.05
EGB 240 mg/kg	87.00 ± 5.48^{c}	45.55 ± 3.05^{c}	176.12 ± 15.41^{c}	1.67 ± 0.11^{c}	10.91 ± 0.74
EGB 480 mg/kg	92.08 ± 8.40^{c}	42.22 ± 2.42^{c}	172.78 ± 9.98^{c}	1.69 ± 0.16^{c}	9.53 ± 0.90

HOMA-IR: Homeostatic model assessment for insulin resistance; ISI: Insulin sensitivity index; HOMA-β: Homoeostasis model assessment of β-cell function.
Data are presented as mean ± SEM (n = 5). λ: $P < 0.001$ compared with normal control. c: $P < 0.001$ and b: $P < 0.01$ compared with diabetic control.

Table 2. Effects of *Globimetula braunii* leaf extract (EGB) on the biomarkers of hepatorenal functions in insulin-resistant animals

Groups	Normal control	Diabetic control	Standard control	EGB (120 mg/kg)	EGB (240 mg/kg)	EGB (480 mg/kg)
AST (U/L)	20.95±1.34	76.04±3.37$^{\lambda}$	48.15±3.41^{c}	56.24±2.31^{b}	50.98±3.84^{c}	38.40±1.96^{c}
ALT (U/L)	32.14±1.37	109.47±8.15$^{\lambda}$	50.14±3.01^{c}	68.88±4.35^{c}	61.93±3.85^{c}	47.28±2.42^{c}
ALP (U/L)	130.35±4.19	201.76±6.84$^{\lambda}$	158.76±3.45^{c}	159.28±2.72^{c}	156.6±2.43^{c}	169.84±4.01^{c}
TP (g/dL)	66.04±4.04	46.63±1.83$^{\beta}$	61.44±2.47^{a}	60.88±3.20^{a}	59.89±1.29^{a}	63.11±2.18^{a}
TB (µmol/L)	16.00±0.56	19.27±0.32	15.41±0.62	14.47±0.52	12.58±0.65^{a}	11.79±0.36^{a}
CB (µmol/L)	4.09±0.20	6.92±0.17	4.15±0.11	5.41±0.23	3.58±0.21^{a}	3.80±0.34^{a}
Creatinine (mg/dL)	1.26±0.04	1.53±0.04$^{\lambda}$	1.12±0.03^{a}	1.19±0.01^{c}	1.16±0.01^{c}	1.09±0.02^{c}
Urea (mg/dL)	25.39±3.23	23.50±3.25	24.71±2.10	23.47±1.91	27.82±2.19	30.54±1.08
Uric acid (mg/dL)	1.20±0.01	1.86±0.05$^{\lambda}$	1.33±0.02^{b}	1.49±0.03^{b}	1.48±0.13^{c}	1.33±0.02^{c}

AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; ALP: Alkaline phosphatase; TP: Total proteins; TB: Total bilirubin; CB: Conjugated bilirubin.
Data are presented as mean ± SEM (n = 5). λ: $P < 0.001$ compared with normal control. c: $P < 0.001$ and b: $P < 0.01$ compared with diabetic control.

the different treatments. SOD activity underwent a notable increase in the liver of animals treated with standard ($P<0.001$) and EGB at doses 120 ($P<0.01$), 240 ($P<0.001$) and 480 mg/kg ($P<0.01$), and in the kidneys of rats having received the standard ($P<0.01$) and EGB at doses 120 ($P<0.001$), 240 ($P<0.05$) and 480 mg/kg ($P<0.001$). An increase in GPx activity was recorded in the liver ($P<0.001$) of animals having received different treatments and in the kidneys of animals treated with standard ($P<0.01$) and EGB at doses of 120 ($P<0.05$), 240 ($P<0.01$) and 480 mg/kg ($P<0.001$) (Table 3).

Effects of EGB on kidney histology

The histological section of the kidneys showed normal architecture representing the glomerulus, proximal convoluted tubule, and distal convoluted tubule in all experimental animals (Figure 2).

Effects of EGB on liver histology

Observation of the liver section of normal rats showed a normal appearance presenting the portal vein, the hepatic artery, and the canaliculus (Figure 3). However, untreated insulin-resistant animals presented slight periportal inflammation (thick arrow). Metformin and EGB doses significantly reduced dexamethasone-induced periportal inflammation (Figure 3).

Discussion

Dexamethasone reduces the sensitivity of cells to glucose by decreasing the level of Glut 2 transporters, which would therefore lead to a disruption in the regulation of carbohydrate metabolism in pancreatic cells, inhibit basal uptake, and stimulate the synthesis of glucose in the adipocyte and would increase gluconeogenesis in the liver (29). These various dysfunctions lead to an increase in insulin deficiency/resistance and blood sugar. Diabetes mellitus has long been treated using medicinal plants, which today continue to be accepted by populations as an alternative therapy (30). In this study, the phytochemical evaluation of EGB showed the presence of flavonoids, saponins, phenols, tannins, and triterpenoids, which are compounds with antidiabetic effects. Dexamethasone causes the loss of body mass in normal animals. Indeed, dexamethasone is recognized for its lipolytic and proteolytic activities. The loss of body mass observed would be relative to tissue reserves of proteins and lipids due to the lack of main energy-producing substrates (carbohydrates) (31). The increase in relative body mass observed after the administration of EGB would be due to the regulation of carbohydrate metabolism via the insulin-mimetic or insulin-secretagogue activity of the extract.

The normal animals treated with dexamethasone presented very high blood sugar and insulin levels, which would probably be the consequence of the activity of dexamethasone, which acts by inhibiting the PI3 kinase enzymes responsible for the translocation of Glut 4 and the membrane uptake of glucose (32). However, there is a significant reduction in blood glucose and insulin levels in insulin-resistant animals treated with EGB. These results are consistent with those obtained by Kolefer et al (33) with the aqueous extract of *Ficus vallis-choudae* leaf. Several phenolic compounds were isolated from the *G. braunii* leaves (12,13,14). The hypoglycemia and hypoinsulinemia observed in this study would be the consequences of the presence of these compounds in the *G. braunii* extract. It has been demonstrated that polyphenols and flavonoids cause a drop in blood sugar by reversing the translocation of glucose transporters from the cell membrane to the intracellular compartment, increasing the sensitivity of target cells to insulin, or by reducing hepatic glucose production following inhibition of gluconeogenesis and glycogenolysis (34,35).

Table 3. Effects of *Globimetula braunii* leaf extract (EGB) on oxidative profile in insulin-resistant animals

	Organ	Normal control	Diabetic control	Standard control	EGB 120 mg/kg	EGB 240 mg/kg	EGB 480 mg/kg
MDA (mmol/mg of tissue)	Liver	3.65±0.17	12.81±0.86$^{\beta}$	6.80±0.25^{c}	7.96±1.57^{b}	7.54±0.25^{b}	6.16±0.16^{c}
	Kidney	4.45±0.35	18.53±1.59$^{\lambda}$	6.50±1.54^{c}	13.02±1.07^{a}	10.08±0.78^{b}	10.85±0.85^{b}
CAT (U/mg of tissue)	Liver	248.13±4.73	72.15±4.74$^{\lambda}$	155.78±8.57^{b}	147.90±4.90^{b}	166.90±5.47^{b}	179.69±25.12^{c}
	Kidney	160.58±5.67	67.12±3.12$^{\lambda}$	141.01±2.24^{c}	104.83±4.53^{c}	116.06±2.41^{c}	128.47±3.85^{c}
SOD (U/mg of tissue)	Liver	68.33±3.32	43.12±3.06$^{\lambda}$	65.25±2.11^{c}	60.40±4.90^{b}	72.72±3.03^{c}	64.87±4.11^{b}
	Kidney	163.00±12.82	77.80±5.43$^{\lambda}$	116.56±2.72^{b}	93.78±3.07^{c}	108.52±4.07^{a}	101.83±5.02^{c}
GPx (U/mg of tissue)	Liver	170.78±15.63	39.26±6.43$^{\lambda}$	117.89±4.08^{c}	142.89±3.92c	162.41±4.88^{c}	158.53±4.21^{c}
	Kidney	119.91±1.97	73.86±2.70$^{\lambda}$	99.55±4.79^{b}	93.43±3.69^{a}	100.07±5.45^{b}	113.81±2.99^{c}
GSH (mg/100 g of tissue)	Liver	3.79±0.13	1.12±0.04$^{\alpha}$	1.79±0.03^{c}	2.02±0.08^{c}	1.86±0.09^{c}	1.79±0.15^{c}
	Kidney	9.40±0.40	5.05±0.13$^{\beta}$	6.45±0.55^{a}	5.68±1.41^{a}	6,84±0,41^{a}	5.71±0.47^{a}

MDA: Malondialdehyde; CAT: Catalase; SOD: Superoxide dismutase; GPx: Glutathione peroxidase; GSH: Reduced glutathione.
Values are expressed as mean (n = 5) ± SEM. λ: $P < 0.001$, β: $P < 0.01$, and α: $P < 0.05$ compared with normal control. c: $P < 0.001$, b: $P < 0.01$, and a: $P < 0.05$ compared with diabetic control.

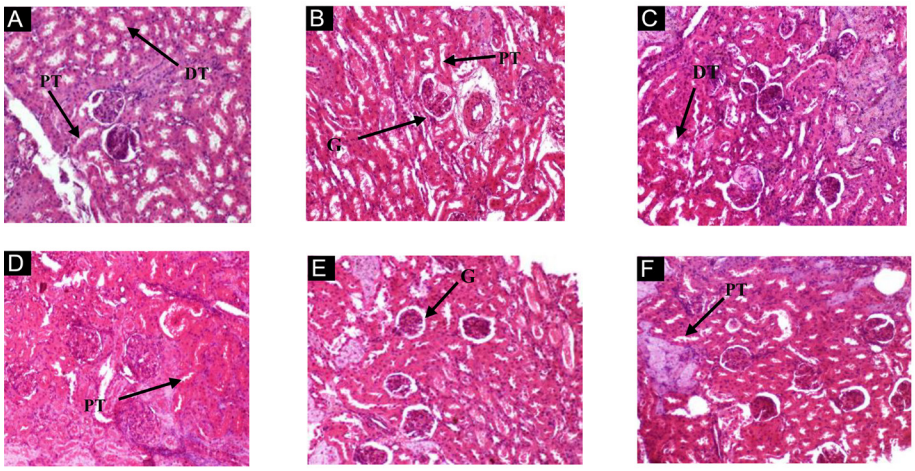

Figure 2. Photographs of the histology of the kidneys of insulin-resistant rats treated with aqueous extract of *Globimetula braunii* leaf (EGB) (H-E, X400). (A) Normal control; (B) Diabetic control; (C) Standard control; (D) EGB 120 mg/kg; (E) EGB 240 mg/kg; (F) EGB 480 mg/kg. G= Glomerulus, DT= Distal convoluted tubule, PT= Proximal convoluted tubule.

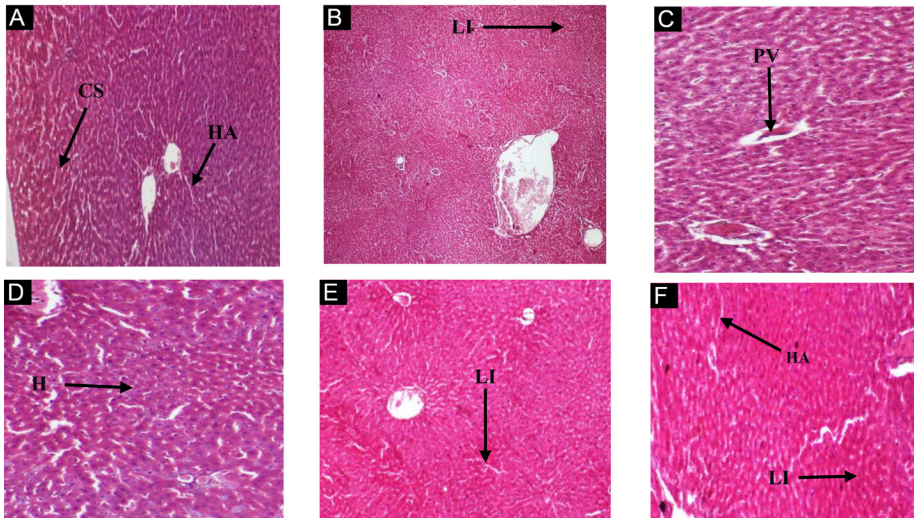

Figure 3. PPhotographs of histological analysis of the liver of insulin-resistant rats treated with Globimetula braunii leaf extract (EGB) (H-E, X400). (A) Normal control; (B) Diabetic control; (C) Standard control; (D) EGB 120 mg/kg; (E) EGB 240 mg/kg; (F) EGB 480 mg/kg. PV= portal vein; H= Hepatocyte; CS= Capillary sinusoid; HA= Hepatic artery; LI= Leukocyte infiltration.

HOMA-IR, HOMA-β, and ISI are indices to assess insulin resistance, pancreatic β function, and insulin sensitivity (36). In our study, we observed an increase in HOMA-IR of untreated insulin-resistant rats and a decrease in ISI, while HOMA-β did not undergo any significant variation, suggesting insulin resistance, the proper functioning of pancreatic β cells, and decreased insulin sensitivity. EGB and metformin significantly reduced HOMA-IR and increased ISI, thus suggesting improvement in the sensitivity of target tissues to insulin.

Liver diseases are common in diabetic patients; hence, the biomarkers of liver function were evaluated in this study. Indeed, transaminases are markers of assessing liver damage, while total proteins and bilirubin are markers of assessing the liver metabolic function (37). AST, ALT, and ALP are sensitive indicators of hepatoxicity because an increase in their activities expresses the degree of liver injury. The increase in the activity of these enzymes in the serum of untreated insulin-resistant animals would be the consequence of the passage of these enzymes from the cytoplasm of hepatocytes to the blood (38). Indeed, chronic hyperglycemia leads to the production of ROS, which can lead to lipid peroxidation, causing liver damage. However, EGB at all doses showed a hepatoprotective potential by reducing the activity of these transaminases in the serum of insulin-resistant rats. Indeed, EGB would have the ability to counteract lipid peroxidation and prevent cellular damage. Maidaidi et al (39) found the results consistent with the present study.

In diabetes, there is an increase in protein catabolism,

which results in the accumulation of amino acids in the liver to produce glucose through gluconeogenesis (40). This proteolysis is due to the non-use of insulin by its target organs due to the decrease in serum total protein concentration observed in untreated insulin-resistant rats. The administration of EGB significantly inhibited proteolysis and regulated the total protein level toward its normal value. Total and conjugated bilirubin levels increase in cases of bile duct damage and hemolysis, respectively (29). In our study, the blood concentrations of total and conjugated bilirubin did not change after EGB administration at doses of 240 and 480 mg/kg. This result suggests that EGB would protect the bile ducts and prevent the bursting of red blood cells.

Urea, creatinine, and uric acid are biomarkers of renal function (41). The increase in these markers in the blood is associated with increased kidney tissue failure. However, rats treated with different doses of EGB produced a significant drop in creatinine and uric acid levels. These results suggest that EGB may have prevented kidney damage.

Diabetes is characterized by chronic hyperglycemia and significant oxidative stress. Oxidative stress is an imbalance between antioxidant and pro-oxidant species in favor of the latter. Oxidative stress will contribute to cellular dysfunction and promote the development of pathologies associated with diabetes (42). Increased blood glucose can induce oxidative stress through the formation of ROS. In the present work, the results showed a significant elevation in the MDA level (end product of lipid peroxidation) in the kidneys and livers in diabetic animals reflecting an increase in lipo-peroxidation, and consequently tissue damage by excessive formation of free radicals (43). The increase in MDA levels could be explained by an imbalance between antioxidant defenses and the production of free radicals in favor of the latter. On the other hand, treatment with metformin and EGB led to a significant drop in MDA levels. This would be due to the beneficial effects of flavonoids, which act by destroying free radicals and inhibiting lipid peroxidation (44). EGB was able to protect kidney and liver tissues against cytotoxic action and oxidative stress induced by dexamethasone. Our results are consistent with several other studies such as those published by Mahamad et al (45) who showed the inhibitory effect of the aqueous extract of *Cissus polyantha* on lipid peroxidation.

GSH is a direct scavenger of free radicals and a necessary co-substrate for GPX activity. In this study, the results revealed decreased renal and hepatic GSH in untreated insulin-resistant animals. This decrease can be due to a deficiency in NADPH, the cofactor of the recycling of GSH from glutathione disulfide (46). The increase in GSH levels obtained after EGB administration would be due to the fact that EGB was able to increase the biosynthesis of glutathione and/or prevent its degradation (47).

GPX, SOD, and CAT are the most important antioxidant enzymes in the body's defense system (48). SOD is an antioxidant enzyme, which catalyzes the disproportionation of the superoxide anion into hydrogen peroxide, thereby reducing the deleterious effects due to free radicals. CAT catalyzes the disproportionation of high concentrations of hydrogen peroxide into oxygen and water, thus protecting tissues from hydroxyl radicals. GPX, via its catalytic activity, allows the degradation of low concentrations of hydrogen peroxides. A significant drop in the activity of SOD, CAT, and GPX was observed in the present study, due to the glycation of these enzymes, which would lead to their inactivation (49). EGB and metformin caused an increase in the activities of these enzymes in the kidney and liver of insulin-resistant animals. Miaffo et al (50) found similar results with *Vitellaria paradoxa* bark. This study suggests that oxidative defense could be reactivated by bioactive compounds present in EGB, which were able to trap free radicals and inhibit pro-oxidant enzymes (51). The stimulation of GPX activity would probably be due to the influence of bioactive compounds present in the plant, such as flavonoids, which would have caused significant synthesis of GSH, a substrate of this enzyme (44).

Histological sections of the kidneys showed normal architecture in all experimental animals. Furthermore, the histology of the liver of untreated insulin-resistant animals showed slight periportal inflammation. On the other hand, the administration of EGB protected the animals' livers against possible damage caused by chronic hyperglycemia.

Conclusion

EGB has hypoglycemic effects and protects the kidney and liver from oxidative damage induced by chronic hyperglycemia. These pharmacological potentials would be linked to flavonoids such as quercetin, catechin, and rutin present in EGB. EGB has remarkable antidiabetic and antioxidant potential, which validates its traditional use as a drug against diabetes mellitus and its complications. To complete this work, we plan, in the future, to elucidate the other mechanisms of actions of *G. braunii* on models of diabetes and evaluate the effects of *G. braunii* on other complications of diabetes.

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Authors' contribution

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Conflict of interests

The authors declare no conflict of interest.

Ethical considerations

All animal experiments were handled according to the Ethics Committee of the Faculty of Sciences of the University of Maroua (Ref. N°14/0261/ Uma/D/FS/VD-RC), Cameroon. The Animal protocol was accomplished in accordance with the guidelines of the Cameroonian bioethics committee (Reg. No. FWA-IRB00001954) and NIH Care and Use of Laboratory Animals manual (8th Edition).

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