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Investigating the ethanolic extract of *Desmodium uncinatum* as a natural protector in streptozotocin-induced diabetic nephropathy in Wistar rats

Jordane W. Kamgaing, Sylviane L. K. Poualeu*, Moïse L. Nchouwet, Lylie G. M. Atsafack, Rostand C. D. Douho, Sylvie L. N. Wansi

Abstract

Background: Diabetic nephropathy is a severe microvascular complication of type 1 diabetes, often leading to chronic kidney disease. This study aimed to evaluate the renoprotective effects of the ethanolic extract of *Desmodium uncinatum* (EEDU) on renal dysfunction in streptozotocin-induced diabetic rats.

Methods: Type 1 diabetes was induced in male rats via intraperitoneal injection of a single dose of streptozotocin (STZ) at 60 mg/kg. After 72 hours, only animals with blood glucose levels above 200 mg/dL were selected for the remainder of the experiment. The rats were treated orally for 28 days with the ethanolic extract of *Desmodium uncinatum* at doses of 91, 182, and 273 mg/kg. The evaluated parameters included body weight, blood glucose, lipid profile, renal function markers (creatinine, albumin, sodium and potassium ions, and glomerular filtration rate), oxidative stress indicators (MDA, SOD, GSH, CAT), pro-inflammatory cytokines (TNF-α, IL-1β), as well as histopathological analysis in kidney tissue.

Results: The extract significantly reduced blood glucose levels ($p < 0.001$) and improved dyslipidemia observed in diabetic rats. It improved renal biomarkers by significantly reducing urinary creatinine ($p<0.01$; $p<0.001$), and urinary protein excretion ($p<0.05$; $p<0.01$). Oxidative stress was alleviated through the significant reduction of malondialdehyde (MDA) levels ($p<0.05$; $p<0.01$; $p<0.001$) and the improvement of superoxide dismutase (SOD) ($p<0.05$) and catalase (CAT) ($p<0.001$) activity. Furthermore, renal tissue analysis of diabetic control rats showed mesangial expansion, leukocyte infiltration, tubular clarification, and tubular sclerosis, which were almost absent in treated rats. A marked decrease in TNF-α and IL-1β ($p < 0.05$; $p< 0.001$) levels was also observed in treated rats' serum.

Conclusion: The ethanolic extract of *D. uncinatum* exhibits both glomerular and tubular protective effects in diabetic nephropathy, likely through its hypoglycemic, hypolipidemic, antioxidant, and anti-inflammatory properties.

Keywords: *Desmodium uncinatum*; Diabetic Nephropathy; dyslipidemia; inflammation; oxidative stress; rats.

*Correspondence: Tel.: +237 698891692; E-mail address: poualeusylviane@yahoo.fr; ORCID: https://orcid.org/0000-0001-5442-3576 (Sylviane L. K. Poualeu)

Research Unit of Animal Physiology and Phytopharmacology, University of Dschang, Dschang, Cameroon

Other authors

E-mail: waguia.jordane@gmail.com (Jordane W. Kamgaing); E-mail: poualeusylviane@yahoo.fr; E-mail: nmlegentil@yahoo.fr; ORCID: https://orcid.org/0000-0002-8025-7716 (Moïse L. Nchouwet); E-mail: giseleatsafack@gmail.com (Lylie G. B. Atsafack); E-mail: douhocyrille@yahoo.fr (Rostand C. D. Douho) E-mail : wansylvie@yahoo.fr, ORCID : https://orcid.org/0000-0002-5584-7095 (Sylvie L. N. Wansi).

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Background

Type 1 diabetes (T1D) is an autoimmune condition in which the immune system progressively destroys pancreatic β-cells, resulting in a complete lack of insulin production [1]. According to the American Diabetes Association [2], diagnosis is confirmed when plasma glucose reaches or exceeds 126 mg/dL. Commonly diagnosed in youth and young adults, T1D is linked to multiple complications, including diabetic nephropathy, a principal contributor to chronic kidney disease (CKD) [3]. In Africa, Adebayo-Gege et al. [4] reported a pooled nephropathy prevalence of 34.2% among diabetic individuals. Chronic kidney disease in the context of T1D arises predominantly from sustained hyperglycemia, which progressively damages both glomerular and tubular structures. This metabolic alteration is amplified by oxidative stress, chronic inflammation, and the accumulation of reactive oxygen species (ROS), all of which compromise renal cellular integrity [5, 6]. Hyperglycemia-induced glomerular hyperfiltration and hypertrophy alter the filtration barrier, while ROS overproduction injures podocytes and tubular epithelial cells, exacerbating nephron loss [7]. Simultaneously, advanced glycation end products (AGEs) accumulate in renal tissues, activating pro-fibrotic and inflammatory cascades such as Nuclear Factor kappa-light-chain-enhancer of activated B cells (NF-κB) and Transforming Growth Factor Beta (TGF-β), thereby promoting glomerulosclerosis and tubulointerstitial fibrosis [8]. Elevated levels of cytokines like tumor necrosis factor alpha (TNF-α) and interleukins 1 beta (IL-1β) intensify renal inflammation and injury [9]. Moreover, chronic activation of the renin–angiotensin–aldosterone system (RAAS) increases intraglomerular pressure and proteinuria, accelerating fibrotic remodeling and CKD progression [10]. Collectively, these combined mechanisms further deteriorate the kidney functions. Despite significant progress in glycemic control and the management of associated risk factors, individuals with T1D remain particularly vulnerable to the development of CKD [11]. Conventional treatments, particularly insulin, have shown limited effectiveness in preventing the progression of renal deterioration, which has increased interest in phytotherapeutic alternatives. Among medicinal plants traditionally used in diabetes management, *Desmodium uncinatum* holds a significant place due to its ethnobotanical use. The metabolites present in *Desmodium uncinatum*, notably genistein, vitexin, and isovitexin, exert significant protective effects against chronic kidney disease. Genistein acts as an antioxidant and anti-inflammatory agent, reducing oxidative stress and renal inflammation [12]. Vitexin inhibits ferroptosis in renal tubular [13]. Isovitexin, through its anti-inflammatory properties, limits renal tissue damage [14]. Until now, no research has investigated the potential nephroprotective properties of *Desmodium uncinatum* in the context of type 1 diabetes. This research therefore aims to assess the impact of its ethanolic extract on metabolic disturbances, oxidative stress, inflammatory markers, and renal histopathological changes in streptozotocin-induced diabetic rats.

Methods

Chemicals

D-glucose and sodium chloride were sourced from the Edu-Lab Biology Kit (Bexwell, UK). A Dutch diagnostic kit was employed to evaluate lipid profile, oxidative stress markers, and urinary biochemical parameters. Serum levels of TNF-α and IL-1β were determined using ELISA kits (R&D Systems, USA) in accordance with the manufacturer's instructions. Specifically, TNF-α was quantified with kit Cat. #DY510, Lot: P166433, and IL-1β with kit Cat. #DY501, Lot: P217832. The Streptozotocin (STZ) (≥98% HPLC, Sigma-Aldrich, Ref. S0130), obtained from HUMEAU Expert du Laboratoire (France). Insulin was provided by Novo Nordisk Production SAS (Chartres, France).

Plant extraction

The entire vegetative parts of *Desmodium uncinatum* were collected by Kamgaing during the raining season of 2022 in Foréké, a locality within the city of Dschang, located in the West Region of Cameroon. Botanical authentication was confirmed by comparison with specimen No. 66950/HNC housed at the National Herbarium of Cameroon. The ethanol extract was obtained by macerating 412 g of *D. uncinatum* powder in 4 liters of 95% ethanol. The mixture was filtered 48 hours later, and the filtrate was concentrated at 65°C using a rotary evaporator set at 78°C. Complete evaporation yielded 26.858 g of a greenish paste, corresponding to an extraction yield of 6.51%. The different extracts were stored in a refrigerator at –20°C and used to prepare the extracts at various doses. The therapeutic dose (182 mg/kg) was obtained according to the traditional practitioner's recommendations, and this dose was then framed to have the other two doses.

Induction

Diabetic nephropathy was induced experimentally through a single intraperitoneal injection of streptozotocin (STZ) stabilized in citrate buffer with at pH 4,5 at a dose of 60 mg/kg body weight in rats fasted for 14 hours. To mitigate the risk of acute hypoglycemia, D-glucose was administered orally at 3 g/kg body weight, 24 hours after STZ injection. Fasting blood glucose levels were determined using an ACCU-CHEK® glucometer with compatible test strips seventy-two hours following induction. Animals presenting blood glucose values exceeding 200 mg/dL were considered diabetic and subsequently included in the experimentation.

Distribution and treatment

To evaluate the effects of *D. uncinatum* ethanolic extract on diabetic nephropathy, 42 rats were divided into 7 groups of 6 animals each and treated for 28 days as follows: Group 1 (neutral control): Non-diabetic rats receiving distilled water; Group 2 (neutral control): Non-diabetic rats receiving citrate buffer; Group 3 (negative control): Diabetic rats receiving NaCl; Group 4 (positive control): Diabetic rats treated with insulin (1 IU/kg); Groups 5, 6, and 7: Diabetic rats treated with the ethanolic extract at doses of 91, 182, or 273 mg/kg, respectively. These animals were raised in natural temperatures and light, with free access to drinking water. All treatments were given at a standardized volume of 1 mL/100 g body weight. The ethanolic extract was administered orally, while insulin was delivered intraperitoneally for a period of 28 days. Fasting blood glucose levels were recorded on day 1 and day 28 of treatment. On day 28, animals were transferred to metabolic cages for 24-hour urine collection, and on day 29, they were sacrificed for biochemical and histological analyses.

Sampling

Following the 24-hour urine collection, samples were measured and centrifuged at 3000 rpm for 15 minutes. The resulting supernatant was transferred into Eppendorf tubes and stored at –

20 °C for subsequent analysis of urinary biomarkers, including creatinine, albumin, sodium ions (Na^+), and potassium ions (K^+). Subsequently, the animals were anesthetized by intraperitoneal injection of diazepam (0.2 ml/100 g body weight) and ketamine (0.1 ml/100 g body weight, and blood samples were collected from the abdominal artery using dry tubes. These tubes were also centrifuged at 3000 rpm for 15 minutes, and the separated serum was introduced into Eppendorf tubes and stored at –20 °C for biochemical assays, including total cholesterol, HDL cholesterol, triglycerides, serum creatinine, and pro-inflammatory cytokines. After blood sampling, the kidneys were excised and weighed to determine their relative weights. The right kidney was homogenized in Tris buffer and centrifuged at 3000 rpm for 15 minutes. The resulting supernatant was used for the quantitative analysis of oxidative stress markers, including malondialdehyde (MDA), superoxide dismutase (SOD), catalase (CAT), nitric oxide (NO), and reduced glutathione (GSH). The left kidney was fixed in 10% neutral buffered formaldehyde for subsequent histological processing and microscopic examination.

Lipids evaluation

Serum concentrations of total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), and triglycerides (TG) were determined using a colorimetric method with the commercially available Dutch Diagnostics kit supplied by the GEOCHIM laboratory. Low-density lipoprotein cholesterol (LDL-C) was then estimated using the formula proposed by Richmond [15] and Roeshlau [16] called Friedewald equation:
LDL-C (mg/dL) = TC – (TG / 5) – HDL-C.

Oxidative stress evaluation

The oxidative status of kidneys homogenates was evaluated using several biochemical assays. Nitric oxide (NO) was determined with the Griess reagent following Chang and Zhang [17], while lipid peroxidation was assessed by measuring malondialdehyde (MDA) levels according to Agbor and Odetola [18]. Antioxidant defenses were analyzed through superoxide dismutase (SOD) activity [19]. Catalase activity [20] and reduced glutathione (GSH) content using the modified method of Sehirli et al. [21].

Protocol for IL-1β and TNF-α measurement

Serum levels of TNF-α and IL-1β were determined using ELISA kits (R&D Systems, Cat. #DY510 and #DY501) in accordance with the manufacturer's instructions. In brief, 96-well microplates were coated with diluted capture antibodies and incubated overnight at 4 °C. Following washing and blocking, 100 µL of standards and serum samples were added and allowed to incubate for 2 hours at room temperature. Detection antibodies were then applied and incubated for 1 hour, followed by additional washing steps. Streptavidin-HRP was introduced and incubated for 20 minutes, after which a freshly prepared substrate solution was added and left to react for 30 minutes in the dark. The reaction was stopped with a stop solution, and absorbance was read at 450 nm. Cytokine concentrations were calculated by interpolation from the standard curves.

Histological analysis

The fixed kidney was embedded in paraffin to obtain solid blocks. These blocks were sectioned with a microtome into thin slices of 4–5 µm, mounted on slides. Finally, the sections were stained with hematoxylin–eosin to allow microscopic observation of renal structures. After staining, the slides were dehydrated in three baths of absolute ethanol and cleared in three baths of xylene. A few drops of resin were then applied to the sections, which were covered with glass coverslips for microscopic observation using a digital camera-equipped microscope. Microphotographs and histomorphometric analysis were performed with Digital Microscope Suit 2.0 and Image J 1.3 software.

Statistical analysis

Performed using GraphPad Prism version 8.4.2. Statistical significance was set at $p<0.05$. Data was expressed as means ± standard error of the mean (SEM). One-way ANOVA followed by Tukey's post-hoc test was applied for single-variable comparisons, while two-way ANOVA followed by Bonferroni's post-hoc test was used for multiple-variable analyses.

Results

Impact of different treatments on animal body weight and kidney relative weight

Table 1 illustrates the changes in body weight and relative kidney weight of the experimental animals. A single dose of streptozotocin (60 mg/kg) produced a marked reduction ($p < 0.001$) in both parameters after 28 days of treatment compared with the neutral control group. This decrease was significantly counteracted by insulin as well as by the ethanolic extract of *Desmodium uncinatum* administered at 91 mg/kg.

Effects of ethanolic extract of Desmodium uncinatum on baseline blood glucose levels in streptozotocin-induced diabetic animals

Intraperitoneal injection of STZ at a dose of 60 mg/kg resulted in a significant increase ($p < 0.0001$) in blood glucose levels of the negative (383.66 ± 51.92 mg/dL) group compared with the neutral (101 ± 1.31 mg/dL) and citrate (100.5 ± 1.20 mg/dL) control groups, as shown in Figure 1. In the groups treated with the ethanolic extract, only the doses of 182 mg/kg and 273 mg/kg significantly ($p<0.05$; $p < 0.001$) reduced blood glucose levels (in diabetic rats, with respective reduction rates of 37.15% (276.83 ± 66.91 mg/dg) and 50.73% (217 ± 33.04 mg/dL). A reduction of 33.75% (291.83 ± 61.52 mg/dL) in blood glucose was observed in animals treated with insulin.

Effects of ethanolic extract of Desmodium uncinatum on some parameters of renal function in diabetic rats

Table 2 presents the effects of the ethanolic extract of *Desmodium uncinatum* on renal function biomarkers, including serum and urinary creatinine, urinary albumin, albumin-to-creatinine ratio, electrolyte excretion (Na^+, K^+), and glomerular filtration rate (GFR). Administration of STZ significantly impaired renal function in diabetic rats, as indicated by elevated serum creatinine, urinary sodium and potassium, and albumin levels, alongside a marked reduction in GFR and the albumin/creatinine ratio. Treatment with insulin and the ethanolic extract of *D. uncinatum* at 91 mg/kg and 182 mg/kg effectively reversed these alterations. Indeed, the extract have enhanced urinary creatinin excretion while significantly reducing serum creatinine, urinary albumin, and the albumin/creatinine ratio. Additionally, both treatments attenuated

electrolyte losses, with the 91 mg/kg, demonstrating the most pronounced effects.

Effects of ethanolic extract of Desmodium uncinatum on lipid profile in diabetic animals

Table 3 summarizes the effects of ethanolic extract of *Desmodium uncinatum* on biochemical parameters (ALT, AST, total cholesterol, HDL, LDL, triglycerides). Streptozotocin markedly increased total cholesterol, LDL, and triglycerides, while reducing HDL in diabetic rats. Insulin and D. uncinatum extracts significantly improved these alterations, with the ethanolic extract at 273 mg/kg showing the strongest effects: a 36.29% reduction in total cholesterol, a 41.5% rise in HDL, and up to 36.60% decrease in LDL. Triglycerides were also lowered by all treatments, except the ethanolic extract at 273 mg/kg, which showed no significant effect.

Effects of ethanolic extract of Desmodium uncinatum on inflammatory parameters on diabetic rats

Table 4 highlights the effects of the ethanolic extract of *Desmodium uncinatum* on serum IL-1β and TNFα levels. Streptozotocin administration significantly increased ($p < 0.0001$) these cytokines in diabetic animals compared with the neutral control. Conversely, insulin ($p<0.05$; 0.001) and the different extract doses significantly reduced ($p < 0.001$) these parameters. The most pronounced effects were observed with insulin and the ethanolic extract at 273 mg/kg, which lowered IL-1β levels by 70.22% and 69.64%, respectively. For TNFα, the strongest reduction (60.54%) was achieved with the ethanolic extract at 91 mg/kg.

Effects of ethanolic extract of Desmodium uncinatum on some oxidative stress parameters on diabetic animals

The effects of ethanolic extract of *Desmodium uncinatum* on renal tissue stress parameters are reported in Table 5. Streptozotocin administration significantly reduced ($p<0.01$) catalase (CAT) activity and glutathione levels in diabetic rats compared to neutral controls. Treatment with insulin and EEDU at 91 and 273 mg/kg doses significantly reversed these effects, by improving antioxidant markers by up to 85%. SOD activity remained unchanged in diabetic control; however, it was increased (118.09%) in the groups receiving the ethanolic extract at the dose of 182 mg/kg. Moreover, MDA levels, elevated by STZ ($p<0.001$), were significantly reduced by all treatments, particularly the 273 mg/kg extract (43.48%). No significant changes were observed in renal nitric oxide levels after 28 days of treatment.

Effect of ethanolic extract of D. uncinatum on kidney histomorphology

Compared to the normal control group, animals in the negative control group exhibited renal alterations, including tubular cell hypertrophy, leukocyte infiltration, tubular sclerosis, tubular clarification (Figure 2). In contrast, animals treated with ethanolic extract at various doses, as well as those receiving the reference substance, showed signs of renal tissue reorganization approaching the architecture observed in the normal control group.

Discussion

Chronic kidney disease is one of the complications of T1D due to interactions between hyperglycemia, dysregulation of lipid metabolism, oxidative stress, and inflammation [22]. In this study, the administration of a single dose (60 mg/kg) of STZ have created diabetic nephropathy, including metabolic dysregulation, glomerular dysfunction, and elevated pro-inflammatory cytokines.
Streptozotocin is widely employed to induce experimental diabetes. It caused pancreas-specific cytotoxic action on pancreatic β-cells primarily via deoxyribonucleic (DNA) alkylation, oxidative stress, and nitric oxide liberation, thereby leading to insulin deficiency [23]. Insulin deficiency reduces glucose utilization in peripheral tissues, leading to hyperglycemia. To satisfy energy demand, the organism shifts towards lipolysis and proteolysis, thus resulting in severe body weight loss and catabolic state of metabolism [24]. Diabetic rats present persistent hyperglycemia as well as body weight loss, which is an indicator of severe metabolic imbalance. Administration of extract of *D. uncinatum* corrected those values by reducing blood glucose and stimulating weight gain.
The diabetic rats in this study have exhibited dyslipidemia characterized by the augmentation of triglyceride, total cholesterol, and low-density lipoprotein cholesterol (LDL-C) levels but reduced high-density lipoprotein cholesterol (HDL-C) levels. These lipid disturbances can't only be attributed to low insulin level but participate also in renal injury. Recently, Chen *et al*. [25] have shown that lipid accumulation in renal tubular epithelial cells induces mitochondrial damage and apoptosis, causing tubular reabsorption disorder and proteinuria. Similarly, Martinez-Péres *et al*. [26] confirmed that hypercholesterolemia accentuates renal endothelial dysfunction by pertubating the signalization of nitric oxide and stimulate oxidative stress. The oxidative stress initiates pro-inflammatory cascades, throw the NF-κB signaling pathway, all this aggravates glomerular and tubulointerstitial damage [27]. In our study, the EEDU have significantly improved lipid profile, demonstrating their protective effect against kidney damage induced by lipid imbalance.
In this study, diabetic control group has exhibited albuminuria, elevated serum creatinine, elevated albumin/creatinine ratio, and reduced of GFR. These abnormalities are major indicators of progressive glomerular injury in CKD [28]. Albuminuria is a manifestation of increased glomerular permeability caused most often by podocyte injury and thickening of the basement membrane. It thus triggers pro-fibrotic and inflammatory signaling, that of NF-κB and TGF-β1/Smad3 [28, 29]. Hypercreatinemia is a manifestation of defective filtration rate and nephron loss, which can lead to kidney dysfunction [30]. STZ-induced hyperglycemia damages the tubular transporter function primarily Na^+/K^+-ATPase which the consequence is the increase of potassium and sodium lost as observed in this study. EEDU treatment has significantly enhanced renal function by reducing albuminuria, serum creatinine, and albumin/creatinine ratio, and correcting electrolyte homeostasis. Histological analysis also confirmed that result because leukocyte infiltration, sclerotic and tubular clearance observed in untreated diabetic rats were significantly reabsorb in the groups treated with the extract, proving recovery of renal function and structure. In streptozotocin-treated diabetic rats, an increase in the level of MDA, reduced activity of SOD and CAT, and reduced activity level of GSH was observed and that revealed an imbalance between antioxidant defense and reactive ROS production. Under these conditions of oxidative stress, lipid peroxidation, mitochondrial injury, and damage to DNA are accentuate and lead to glomerular and tubular injury [31]. At

the same time, excessive levels of pro-inflammatory cytokines TNF-α and IL-1β found in this study could indicate a chronic inflammatory state that enhances renal damage via NF-κB and other pathways of inflammation signaling [29]. Treatment with the extract of *D. uncinatum* lowered significantly oxidative and inflammatory markers by reducing cytokines and MDA, restoring antioxidant enzyme activity. These protective effects can be attributed to genistein, isovitexin and vitexin found in this plant. It has been shown that these compounds exert their nephroprotective effects by modulating key molecular pathways: vitexin activates NRF2, inducing antioxidant enzymes and inhibiting renal ferroptosis and pyroptosis [12, 32]; isovitexin blocks the NF-κB pathway, reducing pro-inflammatory cytokines and mitochondrial apoptosis, thereby protecting against nephrotoxicity [14]; and finally, genistein regulates the TGF-β/Smad pathway, limiting fibrosis and oxidative stress, and improving renal function [11].

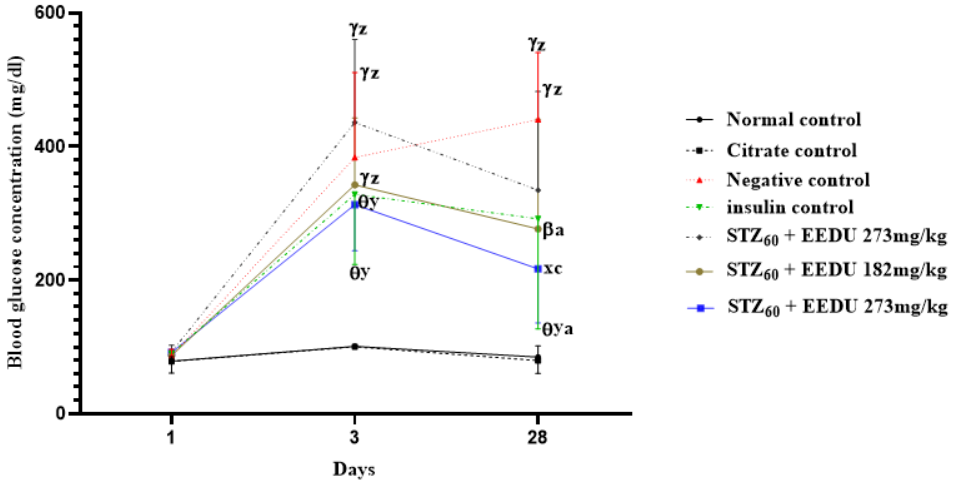

Figure 1. Effects of ethanolic extract of *D. uncinatum* on blood glucose levels in diabetic animals

EEDU: Ethanolic extract of *Desmodium uncinatum*; STZ 60: streptozotocin at the dose of 60mg/kg. βp < 0.01; θp < 0.001; γp < 0.0001: Significant difference compared to the neutral control; xp < 0.01; yp < 0.001, zp < 0.0001: Significant difference compared to the citrate control; ap<0.05; cp < 0.001: Significant difference compared to the negative control. Each bar represents the mean ± SEM of 6 rats per group.

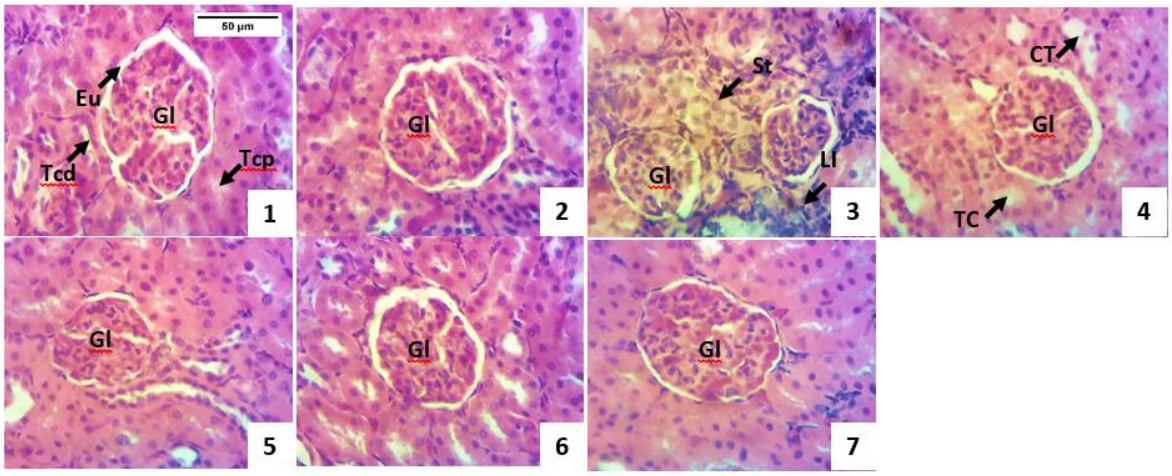

Figure 2. effect of *Desmodium uncinatum* ethanolic extract on kidney histopathology (250 X) Coloration à l'hématoxyline-éosine

1 = Normal control; 2 = Citrate control; 3= Negative control; 4 = Positive control; 5, 6, 7 = Groups receiving the EEDU extract at respective doses of 91, 182, and 273 mg/kg; Gl = Glomerulus Es = Urinary space Dct = Distal convoluted tubule Pct = Proximal convoluted tubule; Tc = Tubular clarification St = Sclerotic tubular; LI: leukocytes infiltration.

Table 1. Effects of ethanolic extract of *Desmodium uncinatum* on body weight and kidney relative weight

Treatments	Doses	Body weight	Kidney relative weight
Normal control	-	118.1 ± 6.40	0.90 ± 0.03
Citrate control	-	117.3 ± 5.02	0.99 ± 0.03
Negative control	-	68.83 ± 6.52**θz**	0.51 ± 0.009 **θz**
Insulin control	1 (IU/kg)	102.2 ± 6.83**b**	0.95 ± 0.10**c**
EEDU	91(mg/kg)	91.77 ± 0.92**a**	0.72 ± 0.07**a**
	182 (mg/kg)	85.33 ± 1.80	0.75± 0.09**b**
	273 (mg/kg)	89.09 ± 3.28	0.78 ± 0.07**a**

EEDU: Ethanolic extract of D*esmodium uncinatum*; STZ 60: streptozotocin; θp < 0.001: significant difference compared to the neutral control. yp < 0.001: significant difference compared to the citrate control; ap < 0.05; bp < 0.01; cp<0.001: significant difference compared to the negative control. Each bar represents the mean ± sem of 6 rats per group.

Table 2: Effects of ethanolic extract of *Desmodium uncinatum* on renal function in diabetic animals

Groups	Normal control	Citrate control	Negative control	Insulin control	STZ_{60} + EEDU91mg/kg	STZ_{60} + EEDU182mg/kg	STZ_{60} + EEDU273mg/kg
Serum Creatinin (mg/l	1.35±0.11	1.08±0.20	2.81±0.27**θz**	1.66±0.20**b**	2.46±0.17**βz**	2.63±0.23**θz**	2.81±0.10**θz**
Urinary Creatinin (mg/l)	120.9±3.64	97.95±4.71	46.74±3.74**θz**	77.08±4.12**θb**	84.56±8.72**c**	82.40±5.35**c**	78.19±5.23**b**
Albumin (g/dl)	0.04±0.003	0.06±0.009	0.13±0.01**θz**	0.03±0.009**c**	0.08±0.005**b**	0.08±0.006**a**	0.08±0.01**b**
Alb/Crea	0.0004±0.0005	0.0006±0.0001	0.002±0.0004**γz**	0.0005±0.0001c	0.001±0.0009**c**	0.001±0.0001**c**	0.001±0.0003**c**
Sodium (mmol/L)	82.7±6.57	75.39±6.51	127.8±4.77**θz**	83.06±5.30**c**	109.0±4.10**αy**	122.2±5.07**γz**	90.74±7.34**c**
Potassium (mmol/L)	88.33±2.71	92.33±3.65	105.1±1.38**γw**	94.14±1.59**a**	93.00±2.28	97.89±1.57	82.94±3.08**c**
GFR (ml/min)	0.44±0.02	0.44±0.02	0.26±0.004**γz**	0.39±0.20	0.36±0.01	0.37±0.02	0.34±0.03

EEDU: Ethanolic extract of *Desmodium uncinatum*; STZ 60: streptozotocin at the dose of 60mg/kg; αp < 0.05 βp < 0.01; θp < 0.001; γp<0.0001: Significant difference compared to the neutral control; wp < 0.05; yp < 0.001; zp<0.0001: Significant difference compared to the citrate control; ap < 0.05, bp < 0.01 cp < 0.001: Significant difference compared to the negative control. Each bar represents the mean ± SEM of 6 rats per group.

Table 3. Effects of ethanolic extract of *Desmodium uncinatum* on the lipid profile of diabetic animals

Groups	Normal Control	Citrate Control	Negative Control	Insulin Control (1 UI/kg)	STZ_{60} + EEDU91mg/kg	STZ_{60} + EEDU182mg/kg	STZ_{60} + EEDU273mg/kg
Total-C (mg/dL)	3.94±0.24	5.77±0.47	7.44±0.51**θ**	5.15±0.33**b**	4.81±0.48**c**	4.98±0.42**b**	4.74±0.24**c**
HDL-C (mg/dL)	30.13±2.07	27.65±1.87**α**	17.98±0.67**θx**	24.34±0.82	25.43±0.90	24.19±0.42	28.31±1.02**c**
LDL-C (mg/dL)	4.15±0.37	4.98±0.21	6.53±0.59**β**	4.39±0.37**b**	4.24±0.49**b**	4.41±0.41**a**	4.16±0.24**b**
Triglyceride (mg/dL)	58.42±2.77	56.90±3.09	99.05±4.34**θz**	53.82±1.31**b**	70.04±4.70**b**	69.09±4.28**c**	78.75±4.19**θy**

EEDU: Ethanolic extract of *Desmodium uncinatum*; STZ 60: streptozotocin at the dose of 60mg/kg; αp < 0.05; βp < 0.01; θp < 0.001: Significant difference compared to the neutral control; xp < 0.01; yp < 0.001; zp<0.0001: Significant difference compared to the citrate control; ap < 0.05; bp < 0.01; cp < 0.001: Significant difference compared to the negative control. Each bar represents the mean ± SEM of 6 rats per group.

Table 4. Effects of ethanolic extract of *D.uncinatum* on IL-1β and TNFα.

Treatments	Doses	IL-1β	TNFα
Normal control	-	32.45 ± 5.89	10.02 ± 3.54
Citrate control	-	73.55 ± 2.80	22.42± 16.66
Negative control	-	396.2 ± 43.91**θy**	56.23 ± 7.03**θy**
Insulin	1 (IU/kg)	118.00 ± 8.65**c**	32.31 ± 2.13**αb**
	91(mg/kg)	159.7 ± 23.98**xc**	22.18 ± 3.96**c**
EEDU	182 (mg/kg)	127.7 ± 18.89**αc**	24.84 ± 5.52**c**
	273 (mg/kg)	120.3 ± 10.97**c**	25.10 ± 2.70**c**

EEDU: Ethanolic extract of *Desmodium uncinatum*; STZ 60: streptozotocin at the dose of 60mg/kg; αp < 0.05; θp < 0.001: Significant difference compared to the neutral control; xp < 0.01, yp < 0.001: Significant difference compared to the citrate control; bp < 0.01; cp < 0.001: Significant difference compared to the negative control. Each bar represents the mean ± SEM of 6 rats per group.

Table 5. Impact of the Ethanolic extract of *Desmodium uncinatum* on Oxidative Stress Biomarkers

Group	Normal control	Citrate Control	Negative control	STZ_{60}+Ins (1 UI/kg)	STZ_{60} + EEDU91 mg/kg	STZ_{60} + EEDU182mg/kg	STZ_{60} + EEDU273mg/kg
CAT (µmol/g tissue)	0.27±0.04	0.33±0.04	0.04±0.01**βy**	0.26±0.05**b**	0.12±0.12**x**	0.23±0.05	0.38±0.07**c**
GSH (µmol/g tissu)	5.06±0.59	5.04±0.83	2.66±0.19**βx**	3.97±0.36	3.32±0.19	4.15±0.36**α**	3.15±0.20**β**
SOD (µmol/g tissue)	40.21±5.3	30.50±2.89	24.15±1.18	26.65±2.66	35.67±11.08	52.67±11.08**a**	33.28±3.08
MDA (µmol/g tissue)	0.18±0.03	0.23±0.03**α**	0.43±0.02**θw**	0.22±0.01**b**	0.23±0.03**b**	0.26±0.05**a**	0.20±0.01**c**
NO (µmol/g tissue)	26.75±1.94	28.84±2.42	22.06±1.33	26.42±4.14	25.81±4.29	28.49±3.40	28.56±1.03

EEDU: Ethanolic extract of *Desmodium uncinatum*; STZ 60: streptozotocin at the dose of 60mg/kg; αp < 0.05; βp < 0.01; θp < 0.001: Significant difference compared to the neutral control; wp < 0.05; xp < 0.01, yp < 0.001: Significant difference compared to the citrate control; ap < 0.05, bp < 0.01; cp<0.001: Significant difference compared to the negative control. Each bar represents the mean ± SEM of 6 rats per group.

Conclusion

In conclusion, this study highlights the therapeutic potential of *Desmodium uncinat*um in diabetic nephropathy, owing to its bioactive compounds and rich phytochemical profile. The observed improvements in metabolic, renal, oxidative, and inflammatory parameters confirm its protective action and support its relevance as a complementary approach in preventing and managing diabetes-related renal complications.

Abbreviations

CKD: Chronic Kidney Disease

D.uncinatum: *Desmodium uncinatum*
TNF-α : Tumor necrosis factor alpha
IL-1β : Interleukin 1 beta
TGF-β: Transforming Growth Factor Beta
ROS : reactive species of oxygen
NO : nitric oxide
DNA : deoxyribonucleic acid
CAT : Catalase
GSH : reduced glutathione
SOD : superoxide dismutase
NF-κB: Nuclear Factor kappa B
TGF-β/Smad: Transforming Growth Factor Beta (TGF-β)

Authors' Contribution

JKW, SLKP and SLNW conceived and designed the study. JKW, LGMA, RCDD collected and analyzed the data. JKW, SLKP, MLN, LGMA and SLNW drafted the manuscript and critically revised it for important intellectual content. All authors approved the final version of the manuscript and agree to be accountable for all aspects of the work.

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Conflict of interest

The authors declare no conflict of interest

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