The Thai Journal of Pharmaceutical Sciences

Volume 47 | Issue 2 Article 6

April 2023

Phytochemical screening, antihyperglycemic, antihyperlipidemic, and antioxidant activities of parts of Cleome rutidosperma: A comparative study

Israel Oghenevwodokohwo Okoro

Ifeanyi Famous Ossamulu

Edith Omozefe Okoro

Original Article

Thai Journal of Pharmaceutical Sciences

Phytochemical screening, antihyperglycemic, antihyperlipidemic, and antioxidant activities of parts of *Cleome rutidosperma*: A comparative study

Israel Oghenevwodokohwo Okoro[1], Ifeanyi Famous Ossamulu[2], Edith Omozefe Okoro[3]

[1]Department of Biochemistry, Delta State University, Abraka, Delta State, Nigeria, [2]Department of Biochemistry, School of Natural and Applied Science, Federal University of Technology, Minna, Niger State, Nigeria, [3]Department of Medical Biochemistry, College of Medicine, Delta State University, Abraka, Delta State, Nigeria

Corresponding Author:
Israel Oghenevwodokohwo Okoro, Department of Biochemistry, Delta State University, Abraka, Delta State, Nigeria.
Tel: +2348036780386.
E-mail: israelik@yahoo.com

Received: December 31, 2021
Accepted: June 21, 2022
Published: June 30, 2023

ABSTRACT

Background/Aim: *Cleome rutidosperma* is traditionally used as a remedy for several diseases such as diabetes and malarial. The phytochemical screening and influence of hydroethanol extracts of *C. rutidosperma* parts (leaves and roots) on hyperglycemia, hyperlipidemia, and parameters of oxidative stress in streptozotocin (STZ)-induced diabetes in male albino rats were investigated. **Materials and Methods:** Qualitative phytochemical assays for the extracts were done by standard procedures. Different doses (75, 150, and 300 mg/kg body weight) of the extracts were administered to STZ-induced diabetic rats. **Results:** The presence of Alkaloids, Flavonoids, Saponins, Tannins, steroids, Terpenoid, Cardiac glycoside, and Phenol was detected in the leaves, while all the phytocomponent determined, except alkaloids, cardiac glycoside, and phenol were detected in the root extract in varying degrees. The induction of diabetes led to a significant ($P < 0.05$) rise in blood glucose level and marked disturbances of the biochemical parameters assessed, in the STZ-induced diabetic rats. However, treatment with different doses of *C. rutidosperma* extracts caused a significant ($P < 0.05$) reverse in blood glucose level, and the serum and tissues (livers and kidneys) biochemical parameters that were examined to be near normal. **Conclusion:** The results displayed significant anti-hyperglycemic, anti-hyperlipidemic, and antioxidant properties of both extracts dose dependently, with the leaves extracts comparatively displaying better activity than the extract of the root.

Keywords: Antioxidant, *Cleome rutidosperma*, hyperglycemia, hyperlipidemia, phytochemistry

INTRODUCTION

Diabetes mellitus (DM) is a common metabolic disorder of carbohydrate, protein, and fat digestion resultant from a deficiency of insulin secretion/action or both. It is characterized by raised blood levels of glucose, and oxidative stress. Lessened insulin secretion, lesser glucose utilization, and higher production of glucose are among the causal factors to hyperglycemia.[1] The autoimmune damaging activity of beta cells is known to cause insulin dearth and later development of diabetes.[2] Oxidative stress, resultant from reactive oxygen species, has been stated to be involved in the diminishing of β-cell function, hence playing a critical part in the pathology of DM. The Islets of β-cells are decidedly vulnerable to oxidative stress due to their decreased levels of endogenous antioxidants.[3] Chronic ailments have been on the increase, becoming a grave danger to human health and quality of life/life expectancy. Contemporary studies have stated that 451 million people age, 18–99 years experienced DM, universally, in 2017, projecting that this number may increase to 693 million in 2045.[4]

At present, a blend of insulin injections and diet modifications or usage of oral hypoglycemic medications is the leading methods used in controlling hyperglycemia and other diabetes-related complications. Nevertheless, roughly all of the drugs in use are linked with some form of side effect or the other, thus necessitating the continuous search for effective and affordable natural products with nominal side effects to replace currently available antidiabetic drugs.[5]

Cleome rutidosperma DC, commonly known as Fringed Spider Flower, is an herb of the *Capparidaceae* family that grows up to 70 cm with small violet-blue flowers and is found on wastelands and grassy spaces. The plant originated from West Africa and it is also found in different parts of tropical America and South East Asia.[6]

The medicinal properties of the different parts of *C. rutidoaperma* have been reported. Bidla,[7] stated the antiplasmodial activity of its leave extract, while anti-inflammatory, antipyretic, diuretic, laxative, antioxidant, free radical scavenging, analgesic, antimicrobial, and wound healing activities of its aerial parts have been reported.[8,9] The use of the plant in the management of paralysis, skin disease, epilepsy, convulsions, and spasm has also been reported.[10] Similarly, Mondal *et al*.,[11] stated the hypoglycemic effect of its roots, whereas the extracts and fractions of its leaves have been shown to display antioxidant, antihyperglycemic, and antihyperlipidaemic effects.[6,12,13] Although, the medicinal properties of the leaves and aerial parts of the plant have been reported by several researchers, there is a dearth of information on the medicinal properties of its roots.

Therefore, this study was aimed at comparatively evaluating the influence of hydro ethanol extracts of *C. rutidosperma* parts (leaves and roots) on hyperglycemia, hyperlipidemia, and parameters of oxidative stress in Streptozotocin (STZ)-induced diabetes in Wistar male albino rats.

MATERIALS AND METHODS

Reagents and Chemicals

STZ and glibenclamide used in this study were procured from Sigma Chemicals (St Louis U.S.A), while Randox diagnostic kits (for lipid profile, liver, and kidney function tests) were obtained from Randox Laboratories Ltd., UK, and all other reagents and chemicals were of analytical rating.

Sample Collection, Preparation, and Extraction

C. rutidosperma plant was collected from farmland in Abraka, Delta State, Nigeria, and identified by Dr. H. A. Akinnobosun of plant biology and biotechnology, University of Benin, Nigeria, with ref. no. UBHc0148. The samples were separately cleaned, air-dried for 10 days, and homogenized into a fine powder by mortar and pestle. About 20 g of the powdered sample was extracted at room temperature with 200 mL of hydroethanolic (1:1v/v) for 48 h, filtered using Whatman No. 1 filter paper and rotary evaporated to dryness at reduced pressure. The extracts were thereafter stored in airtight bottles at 4°C until used.

Phytochemical Screening

The qualitative phytochemical assays were done by the procedures described earlier,[14,15] to determine the presence of alkaloids, flavonoids, saponins, tannins, steroids, terpenoids, cardiac glycoside, and phenol.

Acute toxicity Studies

The acute toxicity study was done for the extracts, as described earlier to ensure the safe dose to administer to experimental rats.[16] The general health and signs of clinical toxicity in rats were noted during the period, which included rough hair, depression, appetence, and sluggishness.

Animals

Healthy male Albino Wistar rats aged 11 weeks (140–180 g) were procured from the Anatomy department of Delta State University and acclimatized for 2 weeks. The rats were cared for in line with the guiding principles for the use and care of laboratory animals,[17] and with the approval of the research and ethics committee of the faculty of science, Delta State University, Abraka (REL/FOS/21/013). They were fed a standard diet (Growers mash from Top feeds Limited, Sapele, Nigeria) and water *ad libitum* throughout the study. The animals were separated into groups of five rats each as follows:

A = Normal control; B = Diabetic control; C = Diabetic + glibenclamide 5 mg/kg body weight(bw); D = Diabetic + *C. rutidosperma* roots 75 mg/kg bw; E = Diabetic + *C. rutidosperma* roots 150 mg/kg bw; F = Diabetic + *C. rutidosperma* roots 300 mg/kg bw; G = Diabetic + *C. rutidosperma* leaves 75 mg/kg bw; H = Diabetic + *C. rutidosperma* leaves 150 mg/kg bw; I = Diabetic + *C. rutidosperma* leaves 300 mg/kg bw.

Composition of Standard Diet for Rats

S/N	Nutrient	Amount
1	Crude protein	18.00% (min)
2	Fats/oil	5.00% (max)
3	Fiber	8.00% (max)
4	Calcium	1.00% (min)
5	Lysine	1.00% (min)
6	Methionine	0.45% (min)
7	Methionine+Cystine	0.80% (min)
8	Phosphorus	0.40% (min)
9	Available energy	2800 kcal/kg (min)
10	Threonine	0.60% (min)
11	Tryptophan	0.20% (min)

Induction of Diabetes

Diabetes was induced in overnight fasted rats, through a single intraperitoneal shot of 50 mg/kg STZ, dissolved in fresh 0.1 M. cold citrate buffer (pH-4.5). To prevent hypoglycemic shock,

the induced animals were offered 5% glucose in their drinking water for the next 12 h.

After 72 h of diabetes induction, the fasting blood glucose (FBG) level for the rats was evaluated using a glucometer (Accu-Chek), and rats with FBG >250 mg/dl (>13.8 mmol/L) were deemed diabetic and were integrated into this study.

Normal saline, glibenclamide, and the different extracts were given to the animals in groups A/B, C, and D–I daily (once) by gavage for 28 successive days. For FBG measurements, blood samples were collected (from tail vein) on days 0, 7, 14, and 28, which day 0 was collected at 72 h after diabetes induction.

On day 29, rats were fasted for 12 h and sacrificed by cardiac puncture, to obtain the organs (liver and kidney) and serum for the biochemical analysis of this study. The organs were cautiously removed and weighed. About one gram of each organ was subsequently homogenized in 10 mL of phosphate buffer (0.01 M, pH 7.4), and then centrifuged for 10 min at 3000 g to obtain the supernatant, used as the organ extract.

Serum Biochemical Parameters Assessment

Lipid profile parameters were determined as follows: Total cholesterol (TC),[18] high-density lipoproteins (HDL),[19] triglycerides (TRIGS) level,[20] and low-density lipoprotein (LDL).[21]

Liver and kidney function indicators were evaluated, such as alanine transaminase (ALT) and aspartate aminotransferase (AST),[22] alkaline phosphatase (ALP),[23] total protein,[24] total and direct bilirubin levels,[25] urea,[26] and creatinine.[27]

Assessment of Antioxidant Levels

The markers of oxidative stress in the organs (liver and kidney) were determined by standard protocols. Catalase by,[28] Malondialdehyde (MDA) levels by,[29] Superoxide dismutase (SOD) by,[30] while glutathione S-transferase (GST) and tissue protein were assayed by,[31] and[32] methods.

Statistical Analysis

Data obtained were expressed as mean ± SD (Standard Deviation) and analyzed by ANOVA and Tukey Kramer comparison test using Graphpad Prism (version 6.0). $P < 0.05$ was counted statistically significant.

RESULTS

Phytochemical Assessment

The results for the phytochemical screening of hydro ethanol extracts of *C. rutidosperma* (roots and leaves) are presented in Table 1. The presence of eight phytocomponents (alkaloids, flavonoids, saponins, tannins, steroids, terpenoids, cardiac glycosides, and phenol) was detected in the leaves extract in varying degrees, while three of these phytocomponents (alkaloids, cardiac glycoside, and phenol) were not detected in the root extract of the plant. However, five phytocomponents (flavonoids, saponins, tannins, stesteroids, and terpenoid) were noticed in the root extract.

Table 1: Phytochemical screening of hydro ethanol extracts of *C. rutidosperma*

Sample	*C. rutidosperma* roots extract	*C. rutidosperma* leaves extracts
Alkaloids	-	++
Flavonoids	+	++
Saponins	+	++
Tannins	+	+++
Steroid	+	+
Terpenoid	+	+
Cardiac glycosides	-	+
Phenol	-	+

Key: +Slightly present, ++Moderately present, +++Highly present, -Absent, *C. rutidosperma: Cleome rutidosperma*

Oral Acute Toxicity

The oral acute toxicity study for the extracts revealed no toxicity up to 2000 mg/kg/kg body weight of the extracts. Thus, up to this dosage, no adverse impacts or death were discovered, thereby confirming an earlier report on the nontoxicity of the leaves extract and also providing justification for the safety of the root extracts.

Effects of Hydro-ethanol Extract of *C. rutidosperma* Leaves and Roots on FBG Level of STZ Induced Diabetic Rats

As shown in Figure 1, it is the results for the influences of the hydro-ethanol extract of *C. rutidosperma* roots and leaves on FBG levels of STZ-induced diabetic rats. Significant ($P < 0.05$) differences were noticed in the FBG levels between the groups (A–I), on days 14, 21, and 28. On day 0 of treatment, there was no significant difference in the FBG level between the various diabetic groups (B–I). For the diabetic control group, no substantial difference was equally seen between day 0 and day 7 in the FBG level, but significant ($P < 0.05$) differences were noticed in the diabetic control group when its FBG level for day 7 was compared with those of day 14, day 21 and day 28. Thus, there was a steady increase in the FBG level of diabetic control rats from day 7 up to the last day of treatment (day 28). While, a significant decrease ($P < 0.05$) in the FBG level between day 0 and day 7 was noted, in the standard drug group. Furthermore, there was a steady significant decrease ($P < 0.05$) in the FBG between day 7 and day 14, day 21 and day 28. Similarly, no substantial difference was noticed in the FBG between day 0 and day 7 for the group of rats treated with 75 mg/kg of the root extract, but a significant decrease in FBG was noticed in this group, between day 7 and days 14, 21, and 28. Thus, the administration of root extract at the dose of 75 mg/kg was able to significantly ($P < 0.05$) reduce the STZ-induced increase in FBG level. Correspondingly, a steady decrease in FBG level was noticed between day 7 and days 14, 21, and 28, in both root extract and the leaves extract-treated groups, to varying degrees, with the 300 mg/kg leaves extract-treated group giving the highest reduction in FBG among the extracts, on day 28. Therefore, a significant reversal of the STZ-induced FBG increase was seen in all treated groups, with the highest reduction in FBG seen in the standard drug-treated group.

Effects of Hydro-ethanol extract of *C. rutidosperma* Leaves and Roots on Serum Liver Function Parameters

The results for the outcomes of the hydro-ethanol extract of *C. rutidosperma* leaves and roots on serum liver function parameters are shown in Table 2. Significantly ($P < 0.05$) higher activity was seen for serum ALT of the diabetic control group (B) when compared to the normal control and other experimental groups (A, C–I). Furthermore, the ALT activity was significantly ($P < 0.05$), lower in the normal control group than those in Groups D, E, and G. Thus, the induction of diabetes with STZ caused an increase in the serum ALT for the diabetic control group. However, treatment with either the leaves or roots extracts of the plant or the standard drug (glibenclamide) caused a reduction in the serum ALT to near normal. Comparatively, the highest dose (300 mg/kg bw) of the leave extract exhibited the best effect among the extracts for serum ALP. Similarly, the highest serum AST activity was seen in the diabetic control group. Thus, significantly ($P < 0.05$) higher serum AST activity was seen in the diabetic control group, relative to those of groups A, C, F, H, and I. Furthermore, the induction of diabetes produced a significant ($P < 0.05$) surge in the serum ALP activity, as noticed in the serum ALP activity of the diabetic group (B), when compared to other experimental groups. However, treatment with both extracts and the standard drug caused a significant reversal of the increased ALP activity to near normal. Although higher levels of serum total and direct bilirubin were noticed in the diabetic control group (B) relative to other groups, this increase was not significant. Similarly, there was no significant change in the total protein level among the various experimental groups (A–I).

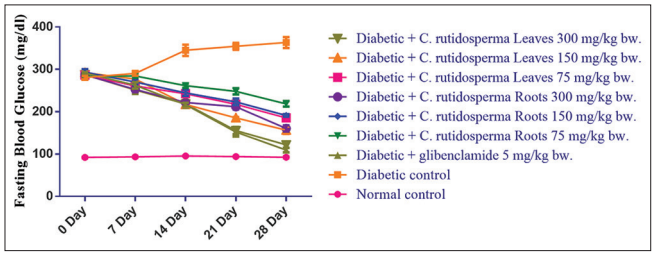

Figure 1: Effects of hydro-ethanol extract of *Cleome rutidosperma* leaves and roots on fasting blood glucose level of rats. *Where day 0 is 72 h after diabetes induction, **Values are Mean ± SD (n=5)

Effects of Hydro-ethanol Extract of *C. rutidosperma* Leaves and Roots on Creatinine and Urea

As shown in Table 3, it is the results for the effects of the hydro-ethanol extract of *C. rutidosperma* leaves and roots on serum creatinine and urea levels in the STZ-induced diabetic rats. The creatinine level for the diabetic control group was significantly higher ($P < 0.05$) compared to Groups A, C, E, and I. Furthermore, higher serum urea level was noticed in the diabetic control group (B), relative to the rest groups (A, C–I). Thus, the diabetes-induced increase in serum urea and creatinine levels was observed to be ameliorated by treatment with the extracts and the standard drug.

Effects of Hydro-ethanol Extract of *C. rutidosperma* Leaves and Roots on Serum Lipid Profile

As presented in Table 4, it is the results for the effects of hydro-ethanol extracts of *C. rutidosperma* leaves and roots on the serum lipid profile of STZ-induced diabetic rats. The TC level in the various experimental groups was in the order: A < I < C < F < H < E < G < D < B, with the level of cholesterol of Group B, being significantly ($P < 0.05$) higher than all other groups. Although the induction of diabetes was associated with an increase in the cholesterol level as seen in the diabetic control group, the administration of either extract for 28 days significantly reduced the level of cholesterol to near normal. On the other hand, a lower HDL value ($P < 0.05$) was obtained from the diabetic control group when compared with either the normal control group or the treated groups in this study. Furthermore, the triglyceride and LDL levels in the diabetic control group were observed to be significantly higher than in the normal control group and the treated experimental groups.

Table 2: Effects of hydro-ethanol extract of *C. rutidosperma* leaves and roots on serum liver function parameters

Group	ALT (U/L)	AST (U/L)	ALP (U/L)	D.BIL (mg/dL)	T.BIL (mg/dL)	TP (mg/dL)
A	23.77 ± 1.94^{a}	43.55 ± 1.49^{e}	70.34 ± 7.10^{i}	0.14 ± 0.02^{p}	0.44 ± 0.03^{q}	8.42 ± 0.83^{r}
B	39.11 ± 4.09^{b}	81.20 ± 2.63^{f}	184.80 ± 8.56^{j}	0.27 ± 0.08^{p}	1.05 ± 0.03^{q}	4.53 ± 0.43^{r}
C	25.41 ± 1.34^{ad}	46.21 ± 1.68^{egh}	80.56 ± 2.08^{k}	0.15 ± 0.02^{p}	0.55 ± 0.07^{q}	8.07 ± 0.45^{r}
D	30.39 ± 1.39^{c}	49.58 ± 0.94^{fgh}	110.71 ± 2.62^{l}	0.19 ± 0.03^{p}	0.88 ± 0.06^{q}	6.48 ± 0.76^{r}
E	28.82 ± 1.44^{d}	48.53 ± 1.13^{fgh}	106.39 ± 4.04^{lm}	0.17 ± 0.04^{p}	0.68 ± 0.03^{q}	6.53 ± 0.30^{r}
F	26.14 ± 0.86^{ad}	46.51 ± 0.89^{egh}	100.90 ± 2.12^{n}	0.16 ± 0.02^{p}	0.45 ± 0.06^{q}	7.15 ± 0.85^{r}
G	29.61 ± 2.42^{cd}	47.69 ± 1.98^{efh}	109.65 ± 1.58^{lm}	0.17 ± 0.01^{p}	0.72 ± 0.07^{q}	6.49 ± 0.73^{r}
H	27.63 ± 1.16^{acd}	44.35 ± 0.79^{eh}	86.78 ± 3.14^{o}	0.16 ± 0.02^{p}	0.66 ± 0.05^{q}	6.84 ± 0.88^{r}
I	22.02 ± 0.52^{a}	44.05 ± 1.65^{eh}	77.34 ± 4.63^{k}	0.15 ± 0.04^{p}	0.52 ± 0.08^{q}	8.78 ± 0.78^{r}

*Values with dissimilar superscripts down a column varies statistically (P<0.05); **Values are Mean±SD (n=5). ***Where Group A=Normal control, B=Diabetic control, C=Diabetic+glibenclamide 5 mg/kg bw; D=Diabetic+C. rutidosperma Roots 75 mg/kg bw.; E=Diabetic+*C. rutidosperma* Roots 150 mg/kg bw; F=Diabetic+*C. rutidosperma* Roots 300 mg/kg bw; G=Diabetic+*C. rutidosperma* Leaves 75 mg/kg bw; H=Diabetic+*C. rutidosperma* Leaves 150 mg/kg bw; I=Diabetic+*C. rutidosperma* Leaves 300 mg/kg bw. ****ALT: Alanine transaminase, AST: Aspartate aminotransferase, ALP: Alkaline phosphatase, D. BIL: Direct bilirubin, T.BIL: Total bilirubin, TP: Total protein, *C. rutidosperma*: *Cleome rutidosperma*

Effects of Hydro-ethanol Extract of *C. rutidosperma* Leaves and Roots on Antioxidant Levels in the Liver of Rats

The results presented in Table 5 are the effects of hydro-ethanol extracts of *C. rutidosperma* leaves and roots on antioxidant levels in the liver of STZ-induced diabetic rats. The liver MDA levels in the experimental groups were in the order: B > D > G > E > H > F > I > C > A, with Group A having a significantly ($P < 0.05$) lower liver MDA level than that of groups B, D, and G. While significantly ($P < 0.05$) higher liver MDA level was noticed in the group B rats relative to the rats in groups A, E, F, H, and I. The activities of SOD, CAT, and GST in the liver of the diabetic control group were significantly ($P < 0.05$) lower than those of the normal control and most of the groups treated with either standard drug or plant extracts.

Table 3: Effects of hydro-ethanol extract of *C. rutidosperma* leaves and roots on creatinine and urea

Group	CREAT (mg/dL)	UREA (mg/dL)
A	1.77±0.58^{s}	19.83±2.55^{u}
B	5.59±0.59^{t}	38.15±4.83^{v}
C	2.05±0.14^{s}	21.35±2.09^{u}
D	2.30±0.46st	25.87±2.35^{wy}
E	2.10±0.05^{s}	22.64±0.63^{u}
F	2.52±0.55st	20.53±1.77^{u}
G	2.88±0.46st	28.24±1.15^{x}
H	2.72±0.52st	24.87±0.87^{y}
I	2.79±0.16^{s}	20.44±1.79^{u}

*Values with dissimilar superscripts down a column varies statistically ($P<0.05$), **Values are Mean±SD ($n=5$), ***Where group A=Normal control; B=Diabetic control; C=Diabetic+glibenclamide 5 mg/kg bw; D=Diabetic+*C. rutidosperma* roots 75 mg/kg bw; E=Diabetic+*C. rutidosperma* roots 150 mg/kg bw; F=Diabetic+*C. rutidosperma* roots 300 mg/kg bw; G=Diabetic+*C. rutidosperma* leaves 75 mg/kg bw; H=Diabetic+*C. rutidosperma* leaves 150 mg/kg bw; I=Diabetic+*C. rutidosperma* leaves 300 mg/kg bw, ****CREAT: Creatinine, *C. rutidosperma*: *Cleome rutidosperma*

Effects of Hydro-ethanol Extract of *C. rutidosperma* Leaves and Roots on Antioxidant Levels in the Kidney of Rats

As shown in Table 6 it is the results of the effects of hydro-ethanol extracts of *C. rutidosperma* leaves and roots on antioxidant levels in the kidney of STZ-induced diabetic rats. The level of MDA in the kidney of Group B rats was observed to be significantly higher ($P < 0.05$) than the value for Groups A, C, and I. Furthermore, significantly ($P < 0.05$) lower kidney SOD activity was noticed in the Group B rats, when compared with those of Groups A, D, F, H, and I. In the same vein, the observed catalase activity in the kidney of diabetic control rats was significantly ($P < 0.05$) lower than the activity displayed in the kidneys of rats in groups A, C, E, F, G, H, and I. Similarly, significantly higher GST activity was observed in the kidney of rats in Groups A, C, D, E, F, H, and I, when they were compared with the diabetic control rats. Thus, treatment with either extract or the standard drug was able to significantly cause a reversal of the diabetes-induced decrease in the GST activity to near normal, with the Group I rats displaying the best activity among the extracts.

DISCUSSION

Hyperglycemia is connected with the production of reactive oxygen species (ROS), initiating oxidative damage, mainly to the liver, heart, and kidney among others. Hyperglycemia surges the assembly of free radicals and declines the tissue antioxidative capability in diabetes. These disproportions result in tissue oxidative stress. To overcome oxidative damage, there is the need to raise tissue antioxidative potential.[33] At present, used oral hypoglycemic medications are linked with some form of side effect or the other, thus necessitating the continuous search for effective and affordable natural products with minimal side effects to replace currently available antidiabetic drugs.[5] This study was aimed at comparatively evaluating the influence of hydro ethanol extracts of *C. rutidosperma* parts (leaves and roots) on hyperglycemia, hyperlipidemia, and parameters of oxidative stress in STZ-induced diabetes in Wistar male albino rats. Results of the study displayed

Table 4: Effects of hydro-ethanol extract of *C. rutidosperma* leaves and roots on serum lipid profile

Group	TC (mg/dL)	HDL (mg/dL)	TRIGS (mg/dL)	LDL (mg/dL)
A	80.53±7.97^{a}	25.52±0.57^{f}	28.00±2.45^{h}	49.41±7.62^{k}
B	162.64±8.52^{b}	17.60±1.53^{g}	92.00±5.10^{i}	127.24±9.9^{l}
C	94.22±3.56^{c}	24.00±1.36^{f}	30.60±1.67^{h}	64.09±3.10^{m}
D	124.44±5.37^{d}	19.62±0.96^{f}	41.60±1.52^{j}	96.56±5.49^{n}
E	112.21±3.75^{e}	21.58±1.46^{f}	40.80±3.35^{j}	82.83±2.39^{o}
F	96.44±3.12^{c}	23.59±1.19^{f}	38.60±1.14^{j}	65.13±3.75^{m}
G	117.37±3.74^{de}	21.87±0.93^{f}	42.80±1.79^{j}	86.98±4.41^{o}
H	108.43±4.62^{e}	22.78±0.70^{f}	39.60±2.61^{j}	77.80±4.44^{o}
I	90.93±2.69^{c}	24.38±0.98^{f}	32.00±2.35^{h}	60.15±3.21^{m}

*Values with dissimilar superscripts down a column vary statistically ($P<0.05$), **Values are Mean±SD ($n=5$), ***Where group A=Normal control; B=Diabetic control; C=Diabetic+glibenclamide 5 mg/kg bw; D=Diabetic+*C. rutidosperma* roots 75 mg/kg bw; E=Diabetic+*C. rutidosperma* roots 150 mg/kg bw; F=Diabetic+*C. rutidosperma* roots 300 mg/kg bw; G=Diabetic+*C. rutidosperma* leaves 75 mg/kg bw; H=Diabetic+*C. rutidosperma* leaves 150 mg/kg bw; I=Diabetic+*C. rutidosperma* leaves 300 mg/kg bw, ****TC: Total cholesterol; HDL: High-density lipoproteins; TRIGS: Triglycerides; LDL: Low-density lipoprotein, *C. rutidosperma*: Cleome rutidosperma

Table 5: Effects of hydro-ethanol extract of *C. rutidosperma* leaves and roots on antioxidant levels in the liver of rats

Group	Liver MDA (nmol/mg protein)	Liver SOD (Units/mg protein)	Liver CAT (Units/mg protein)	Liver GST (Units/mg protein)
A	8.08 ± 1.16^{a}	18.19 ± 0.80^{g}	10.13 ± 0.62^{n}	6.79 ± 0.74^{s}
B	18.00 ± 1.28^{b}	9.38 ± 1.70^{h}	3.80 ± 0.62^{o}	1.05 ± 0.44^{t}
C	9.34 ± 0.47^{a}	16.05 ± 1.00^{g}	8.34 ± 0.81^{np}	5.90 ± 0.95^{svw}
D	13.62 ± 0.92^{bc}	12.38 ± 0.56^{h}	4.29 ± 0.83^{o}	4.10 ± 0.53^{u}
E	11.58 ± 0.75^{acd}	14.25 ± 0.93^{gi}	6.70 ± 0.61^{no}	5.60 ± 0.65^{sxy}
F	10.36 ± 0.72^{acd}	15.69 ± 2.28^{gi}	7.73 ± 0.72^{nop}	5.20 ± 0.57^{uvx}
G	12.63 ± 0.86^{bcd}	13.52 ± 0.38^{ij}	5.22 ± 0.76^{op}	4.10 ± 0.56^{u}
H	10.38 ± 0.58^{ad}	15.42 ± 0.55^{gj}	7.34 ± 0.40^{nop}	4.60 ± 0.61^{uwyz}
I	9.38 ± 0.39^{ad}	16.91 ± 0.67^{gj}	9.72 ± 0.77^{np}	5.60 ± 0.82^{sz}

*Values with dissimilar superscripts down a column varies statistically ($P<0.05$), **Values are Mean±SD ($n=5$), ***Where group A=Normal control; B=Diabetic control; C=Diabetic+glibenclamide 5 mg/kg bw; D=Diabetic+*C. rutidosperma* Roots 75 mg/kg bw; E=Diabetic+*C. rutidosperma* Roots 150 mg/kg bw; F=Diabetic+*C. rutidosperma* Roots 300 mg/kg bw; G=Diabetic+*C. rutidosperma* Leaves 75 mg/kg bw; H=Diabetic+*C. rutidosperma* Leaves 150 mg/kg bw; I=Diabetic+*C. rutidosperma* Leaves 300 mg/kg bw, ****MDA: Malondialdehyde; SOD: Superoxide dismutase; CAT: Catalase; GST: Glutathione S-transferase, *C. rutidosperma*: Cleome rutidosperma

Table 6: Effects of hydro-ethanol extract of *C. rutidosperma* leaves and roots on antioxidant levels in the kidney of rats

Group	Kidney MDA (nmol/mg protein)	Kidney SOD (Units/mg protein)	Kidney CAT (Units/mg protein)	Kidney GST (Units/mg protein)
A	3.65 ± 0.84^{e}	14.46 ± 0.45^{k}	7.45 ± 0.59^{q}	6.03 ± 0.54^{s}
B	19.39 ± 1.65^{f}	6.85 ± 1.23^{l}	2.55 ± 0.82^{r}	0.55 ± 0.28^{t}
C	4.68 ± 0.64^{eh}	13.71 ± 0.78^{km}	7.65 ± 0.61^{q}	4.34 ± 0.75^{u}
D	6.70 ± 0.82^{eh}	8.10 ± 0.70^{l}	2.32 ± 0.85^{r}	2.12 ± 0.52^{vw}
E	5.82 ± 0.75^{eh}	8.27 ± 0.57^{l}	4.33 ± 0.54^{q}	2.20 ± 0.93^{vxy}
F	5.48 ± 0.96^{eh}	11.49 ± 1.39^{km}	4.87 ± 0.51^{q}	3.25 ± 0.64^{uvx}
G	8.82 ± 0.42^{gh}	$9.70\pm0.71l^{m}$	3.98 ± 0.45^{q}	1.84 ± 0.41^{twyz}
H	6.54 ± 0.68^{eh}	$11.93\pm1.16k^{m}$	5.57 ± 0.37^{q}	2.68 ± 0.88^{vz}
I	4.26 ± 0.98^{eh}	13.52 ± 0.64^{km}	6.18 ± 1.05^{q}	3.30 ± 0.89^{uv}

*Values with dissimilar superscripts down a column varies statistically ($P<0.05$), **Values are Mean±SD ($n=5$), ***Where Group A=Normal control; B=Diabetic control; C=Diabetic+glibenclamide 5 mg/kg bw; D=Diabetic+*C. rutidosperma* Roots 75 mg/kg bw; E=Diabetic+*C. rutidosperma* Roots 150 mg/kg bw; F=Diabetic+*C. rutidosperma* Roots 300 mg/kg bw; G=Diabetic+*C. rutidosperma* Leaves 75 mg/kg bw; H=Diabetic+*C. rutidosperma* Leaves 150 mg/kg bw; I=Diabetic+*C. rutidosperma* Leaves 300 mg/kg bw, ****MDA: Malondialdehyde; SOD: Superoxide dismutase; CAT: Catalase; GST: Glutathione S-transferase, *C. rutidosperma*: Cleome rutidosperma

significant anti-hyperglycemic, anti-hyperlipidemic, and antioxidant properties of both extracts in a dose-dependent fashion, with the leaves extracts comparatively displaying better activity than the extract of the roots. Furthermore, the oral acute toxicity study for both extracts showed no observable adverse impacts or death up to 2000 mg/kg body weight. Thus confirming the safety of the extracts.

In this experiment, a significant rise in blood glucose levels was noticed in the diabetic control rats. The rise in glucose level may have resulted from STZ-induced damage to pancreatic β-cells.[34] However, the administration of either the reference drug or the varying doses (75, 150, and 300 mg/kg b.w.) of the extracts daily to STZ-induced diabetic rats for 28 days significantly caused a dose-dependent reduction in the level of FBG relative to the diabetic control group. Thus, the administration of *C. rutidosperma* extracts significantly reduced serum glucose concentration to a near-normal level, with the leaves extract displaying a better hypoglycemic effect than the extract of the root, and the highest dose (300 mg/kg b.w) of either extract giving the highest effect among the doses in each extract. The controlling of blood glucose levels is a foremost approach to the regulation of DM and related complications. The noticed hypoglycemic effect of the extracts agrees with earlier reports on the hypoglycemic effect of its roots and leaves.[6,11-13] The antihyperglycemic action of the extracts may be due to their polyphenols contents. Flavonoids have been reported to raise the peripheral use of glucose and hinder glucose transporter efficiency from the intestine and the potentiation of insulin in beta cells of the Langerhans islets.[35-37]

In this study, the injection of STZ led to a marked disturbance of the biochemical parameters examined in the STZ-control group characterized by significant amplification of the activities of serum liver enzymes (ALT, ALP, and AST). However, treatment with either the leaves or roots extracts of the plant or the standard drug (glibenclamide) caused a reversal in the observed STZ-induced aberration in the serum parameters to near normal. Comparatively, the highest dose (300 mg/kg bw) of the leave extract exhibited the best effect among the extracts. A general increase in ALT, ALP, and ASP activities of diabetic animals has also been reported.[6,38]

Similarly, the injection of STZ in this study led to increasing levels of serum kidney functions markers (urea and creatinine), in the diabetic control rats. However, the administration of hydro ethanol extract of both the leaves and roots of *C. rutidosperma* (75, 150, and 300 mg/kg b.w.) daily caused improvement in all apparent abnormalities in kidney parameters noticed in the diabetic control, which may be attributed to their antioxidant properties. These observations agree with earlier reports on STZ-induced diabetes.[39] The observed raised levels of urea in the STZ-induced diabetic rats may be due to heightened catabolism of both the liver and plasma proteins. The increment in serum creatinine level signifies kidney function impairment.[6,40]

The induction of diabetes by STZ caused significant increments in the level of serum TC, LDL, and TG and a reduction of HDL levels, in this study. However, the treatment of the diabetic rats with either the reference drug or extracts caused an improvement in the levels of these parameters. Lipid profile anomaly, characterized by the increase of TC, LDL, and TG and reductions of HDL, is a normal incidence in DM.[41-43] In this study, treatment with *C. rutidosperma* extracts significantly reduced serum triglycerides and the TC in STZ-induced diabetic rats. Accordingly, it is sensible to conclude that *C. rutidosperma* extracts could moderate blood lipid abnormalities.

In DM, tissue damage is thought to be facilitated by free radicals which attack membranes by the peroxidation of fatty acids.[44] A striking surge in the level of MDA was seen in the liver and kidney tissues of diabetic rats in this study. However, the administration of *C. rutidosperma* extracts and the reference drug significantly reduced the concentration of Thiobarbituric acid reactive substance (TBARS) in the STZ-induced diabetic rats. Thus, in this experiment, the extracts of *C. rutidosperma* significantly mitigated the raised lipid peroxidation level which may be attributed to the antioxidant influence of the flavonoids content of the extract.[45] Hence, the results of this study showed a significantly lower accumulation of lipid peroxidation product in the kidney and liver of the diabetic rats treated with the different doses of the extracts, thereby providing evidence, that intake of these extracts could check oxidative stress in diabetes.

Significant diminishing in the activities of antioxidant enzymes (GST, CAT, and SOD) in the STZ-induced diabetic rats compared with the normal control rats was seen in this experiment in both kidney and liver. However, the administration of the various doses of the extracts for 28 days caused a reversal of this abnormality to near normal with the leaves extracts again displaying better activity in these enzymes when compared with the diabetic control rats. Catalase is a key primary antioxidant defense constituent, which catalyzes the disintegration of H_2O_2 to H_2O. CAT is considered a major kidney antioxidant that aids the reduction of H_2O_2 and defends the tissues from highly reactive hydroxyl radicals. Shortage of CAT activity has been reported to accelerate kidney damage in diabetes by peroxisomal dysfunction.[46] SOD is involved in the scavenging of superoxide radicals ($O_2\cdot-$) and hence precludes its conversion to molecular oxygen and H_2O_2.[47] The observed reduction in SOD activity in the kidney and liver of diabetic rats in this study may be a result of oxidative inactivation through H_2O_2 or glycosylation.[48]

Previously, a marked reduction in GST activity has been stated in the liver, pancreas, and kidney of diabetic rats.[6,49] GST is reported to catalyze the decrease of hydroperoxides and hydrogen peroxide to non-toxic products. Reductions in the activities of CAT, SOD, and GST have also been reported earlier in the kidney and liver tissues of diabetic animals. GST, CAT, and SOD are enzymatic antioxidants that play a crucial role in the prevention of cells from oxidative damage. However, in DM, elevated glucose levels can deactivate these enzymes through glycation thereby inducing oxidative stress that results in lipid peroxidation.[50] In this experiment, the activities of CAT, SOD, and GST were significantly improved to near normal by the administration of the extracts, demonstrating the efficiency of the extracts in mitigating oxidative stress in the kidney and liver of diabetic rats.

The antioxidant and antidiabetic actions of polyphenols and other phytocomponents examined in this study have been reported.[35-37] In this experiment, the phytoconstituents screening of *C.*
presence of flavonoids, terpenoids, and phenolic compounds which are harmonious with the results of previous studies on the plant.[12] Similarly, the antidiabetic activities of these secondary metabolites have been stated.[36,37,51,52] Hence, the antidiabetic effect of the *C. rutidosperma*
study may be due partly to the occurrence of these diverse secondary metabolites and their possible synergistic effects.

CONCLUSION

This study demonstrated that the hydro ethanol extracts of the leaves and roots of *C. rutidosperma*
anti-hyperlipidemic, and *in vivo*
dependently. Comparatively, the leaves extract of the plant demonstrated better promising effects over the extract of the root, which was supported by the results for the phytochemical screening, where more phytoconstituents were detected in the leaves extract when compared with the root extract, lacking the presence of alkaloid, cardiac glycosides, and phenols with reported antidiabetic activity. Thus, the probable mechanism of action of the extracts may be through the synergistic actions of their phytoconstituents. Further, the study is therefore recommended toward isolating the active compound(s) responsible for the antidiabetic property displayed by both extracts of the plant.

CONFLICTS OF INTEREST

We have no conflicts of interest.

REFERENCES

1. Muoio DM, Newgard CB. Mechanisms of disease: Molecular and metabolic mechanisms of insulin resistance and beta-cell failure in type 2 diabetes. Nat Rev Mol Cell Biol 2008;9:193-205.
2. Yoon JW, Jun HS. Autoimmune destruction of pancreatic beta cells. Am J Ther 2005;12:580-91.
3. Azevedo-Martins AK, Lortz S, Lenzen S, Curi R, Eizirik DL, Tiedge M. Improvement of the mitochondrial antioxidant defense status prevents cytokine-induced nuclear factor-kappaB activation in insulin-producing cells. Diabetes 2003;52:93-101.
4. Cho NH, Shaw JE, Karuranga S, Huang Y, da Rocha Fernandes JD, Ohlrogge AW, *et al*. IDF diabetes atlas: Global estimates of

diabetes prevalence for 2017 and projections for 2045. Diabetes Res Clin Pract 2018;138:271-81.
5. Tang X, Olatunji OJ, Zhou Y, Hou X. *Allium tuberosum*: Antidiabetic and hepatoprotective activities. Food Res Int 2017;102:681-9.
6. Okoro IO, Umar IA, Atawodi SE, Anigo KM. Antidiabetic effect of *Cleome rutidosperma* Dc and *Senecio biafrae* (Oliv. and Hiern) extracts in streptozotocin-induced diabetic rats. Int J Pharm Sci Res 2014;5:2480-97.
7. Bidla G, Titanji VP, Joko B, Ghazali GE, Bolad A, Berzins K. Antiplasmodial activity of seven plants used in African folk medicine. Indian J Pharmacol 2004;36:245-6.
8. Bose A, Mondal S, Gupta JK, Ghosh T, Debbhuti D, Si S. Antioxidant and free radical scavenging activities of *Cleome rutidosperma*. Orient Pharm Exp Med 2008;8:135-45.
9. Mondal S, Suresh P. Wound healing activity of *Cleome rutidosperma* DC. roots. Int Curr Pharm J 2012;1:151-4.
10. Kirtikar KR, Basu BD. Indian Medicinal Plants. Dehradun: Lalit Mohan Basu; 1991. p. 181.
11. Mondal S, Dash GK, Acharyya S, Bose A, Singh V. Hypoglycaemic activity from the roots of *Cleome rutidosperma* DC. J Biomed Sci 2009;4:64-9.
12. Okoro IO, Umar IA, Atawodi SE, Anigo KM. Bioassay-guided evaluation of the antidiabetic activity of *Cleome rutidosperma* DC. Int J Pharm Pharm Sci 2015;7:198-202.
13. Okoro IO, Umar IA, Atawodi SE, Anigo KM. *In vitro* and *in vivo* antihyperglycemic effect of active fraction of *Cleome rutidosperma* DC. Int J Pharm Pharm Sci 2015;7:289-95.
14. Harborne JB, Phytochemical Methods a Guide to Modern Techniques of Plant Analysis. Chapman and Hall: New York 1984; p85.
15. Lay MM, Karsani SA, Mohajer S, Abd Malek SN. Phytochemical constituents, nutritional values, phenolics, flavonols, flavonoids, antioxidant and cytotoxicity studies on *Phaleria macrocarpa* (Scheff.) Boerl fruits. BMC Complement Altern Med 2014;14:152.
16. Okoro IO, Umar IA, Atawodi SE, Anigo KM. Comparative antihyperglycemic effect of petroleum ether, acetone, ethanol and aqueous extracts of *Cleome rutidosperma* DC and *Senecio biafrae* (Oliv. and Hiern) in streptozotocin-induced diabetic mice. Br J Pharmacol Toxicol 2014;5:115-24.
17. Olfert ED, Cross BM, McWilliams AA. Guide to the Care and Use of Experimental Animals. 2nd ed. Ottawa, Canada: Canadian Council on Animal Care; 1993. p. 82-93.
18. Allain CC, Poon LS, Chan CS, Richmond W, Fu PC. Enzymatic determination of total serum cholesterol. Clin Chem 1974;20:470-5.
19. Burstein M, Scholnick HR, Morfin R. Rapid method for the isolation of lipoproteins from human serum by precipitation with polyanions. J Lipid Res 1970;11:583-95.
20. Fossati P, Prencipe L. Serum triglycerides determined colorimetrically with an enzyme that produces hydrogen peroxide. Clin Chem 1982;28:2077-80.
21. Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. Clin Chem 1972;18:499-502.
22. Reitman S, Frankel S. A colorimetric method for the determination of serum glutamic oxalacetic and glutamic pyruvic transaminases. Am J Clin Pathol 1957;28:56-63.
23. Belfield A, Goldberg DM. Colourimetric determination of alkaline phos-phatase activity. Enzyme 1971;12:561-8.
24. Henry RJ. Colorimetric determination of total protein. In: Clinical Chemistry. Harper and Row. New York, NY; 1964. p. 181.
25. Walter M, Gerade H. An ultramicromethod for the determination of conjugated and total bilirubin in serum or plasma. Microchem J 1970;15:231-43.
26. Weatherburn MW. Colorimetric method for serum urea determination. Anal Chem 1967;39:971.
27. H. Bartels, M. Böhmer, C. Heierli. Serum kreatininbestimmung ohne enteiweissen. Clinica Chimica Acta 37;1972: 193-197.
28. Beers RF Jr., Sizer IW. A spectrophotometric method for measuring the breakdown of hydrogen peroxide by catalase. J Biol Chem 1952;195:133-40.
29. Varshney R, Kale RK. Effects of calmodulin antagonists on radiation-induced lipid peroxidation in microsomes. Int J Radiat Biol 1990;58:733-43.
30. Fridovich I. Superoxide dismutases. Adv Enzymol Relat Areas Mol Biol 1974;41:35-97.
31. Habig WH, Pabst MJ, Jakoby WB. Glutathione S-transferases. The first enzymatic step in mercapturic acid formation. J Biol Chem 1974;249:7130-9.
32. Bradford MM. A rapid and sensitive method for the quantitation of microgram quantities of protein utilizing the principle of protein-dye binding. Anal Biochem 1976;72:248-54.
33. Fang D, Wan X, Deng W, Guan H, Ke W, Xiao H, *et al.* Fufang Xue Shuan Tong capsules inhibit renal oxidative stress markers and indices of nephropathy in diabetic rats. Exp Ther Med 2012;4:871-6.
34. Palmer AM, Thomas CR, Gopaul N, Dhir S, Anggård EE, Poston L, *et al.* Dietary antioxidant supplementation reduces lipid peroxidation but impairs vascular function in small mesenteric arteries of the streptozotocin-diabetic rat. Diabetologia 1998;41:148-56.
35. Jadhav R, Puchchakayala G. Hypoglycemic and antidiabetic activity of flavonoids: Boswellic acid, ellagic acid, quercetin, rutin on streptozotocin-nicotinamide induced type 2 diabetic rats. Int J Pharm Pharm Sci 2012;4:251-6.
36. Jain S, Pawan Gupta AK. Anti-diabetic activity of ethanol extract of praecitrullus fistulosus leaves on streptozotocin induced diabetic rats. Int J Pharm Sci Res 2017;8:740-5.
37. Tofighi Z, Moradi-Afrapoli F, Ebrahimi SN, Goodarzi S, Hadjiakhoondi A, Neuburger M, *et al.* Securigenin glycosides as hypoglycemic principles of *Securigera securidaca* seeds. J Nat Med 2017;71:272-80.
38. Rodríguez V, Plavnik L, Tolosa de Talamoni N. Naringin attenuates liver damage in streptozotocin-induced diabetic rats. Biomed Pharmacother 2018;105:95-102.
39. Dosch AR, Imagawa DK, Jutric Z. Bile metabolism and lithogenesis: An update. Surg Clin North Am 2019;99:215-29.
40. Alaofi AL. Sinapic acid ameliorates the progression of streptozotocin (STZ)-induced diabetic nephropathy in rats via NRF2/HO-1 mediated pathways. Front Pharmacol 2020;11:1119.
41. Kondeti VK, Badri KR, Maddirala DR, Thur SK, Fatima SS, Kasetti RB, *et al.* Effect of *Pterocarpus santalinus* bark, on blood glucose, serum lipids, plasma insulin and hepatic carbohydrate metabolic enzymes in streptozotocin-induced diabetic rats. Food Chem Toxicol 2010;48:1281-7.
42. Parmar GR, Pundarikakshudu K, Balaraman R. Antidiabetic and antihyperlipidemic activity of *Euphorbia thymifolia* L. extracts on streptozotocin-nicotinamide induced type 2 diabetic rats. J Appl Pharm Sci 2017;7:78-84.
43. Arunachalam K, Parimelazhagan T. Antidiabetic activity of *Ficus amplissima* smith. Bark extract in streptozotocin induced diabetic rats. J Ethnopharmacol 2013;147:302-10.
44. Chandran R, Parimelazhagan T, Shanmugam S, Thankarajan S. Antidiabetic activity of Syzygium calophyllifolium in Streptozotocin-Nicotinamide induced Type-2 diabetic rats. Biomed Pharmacother 2016;82:547-54.
45. Naik SR, Shaikh NS, Patil RR, Somani RS, Mali AS. Protective activity profile of herbomineral medicine in early diabetic nephropathy rats: Restoration of kidney antioxidants, hemodynamics and suppression of proinflammatory mediators. Biomed Aging Pathol 2014;4:33-41.
46. Ravi K, Ramachandran B, Subramanian S. Protective effect of *Eugenia jambolana* seed kernel on tissue antioxidants

in streptozotocin-induced diabetic rats. Biol Pharm Bull 2004;27:1212-7.
47. Hwang I, Lee J, Huh JY, Park J, Lee HB, Ho YS, *et al.* Catalase deficiency accelerates diabetic renal injury through peroxisomal dysfunction. Diabetes 2012;61:728-38.
48. Vincent AM, Russell JW, Low P, Feldman EL. Oxidative stress in the pathogenesis of diabetic neuropathy. Endocr Rev 2004;25:612-28.
49. Sharifi-Rad M, Anil Kumar NV, Zucca P, Varoni EM, Dini L, Panzarini E, *et al.* Lifestyle, oxidative stress, and antioxidants: Back and forth in the pathophysiology of chronic diseases. Front Physiol 2020;11:694.
50. Latha M, Pari L. Effect of an aqueous extract of *Scoparia dulcis* on blood glucose, plasma insulin and some polyol pathway enzymes in experimental rat diabetes. Braz J Med Biol Res 2004;37:577-86.
51. Kennedy AL, Lyons TJ. Glycation, oxidation, and lipoxidation in the development of diabetic complications. Metabolism 1997;46:14-21.
52. Prabhakar P, Banerjee M. Antidiabetic phytochemicals: A comprehensive review on opportunities and challenges in targeted therapy for herbal drug development. Int J Pharm Res 2020;12:1673-96.