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Antioxidant and Antidiabetic Effect of *Capparis decidua* Edgew (Forssk.) Extract on Liver and Pancreas of Streptozotocin-induced Diabetic Rats

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Abstract

Introduction: The twig of *Capparis decidua* has been traditionally used as an antidiabetic agent but its medicinal use has not been scientifically proved yet. The present study evaluated the antidiabetic effect and antioxidant activities of aquatic extract of twig of *C. decidua* on the liver and pancreas of diabetic rats induced by streptozotocin (STZ).

Materials and Methods: The effect of *Capparis decidua* was evaluated by biochemical, histological and Fourier-transform Infrared Spectroscopy (FTIR) studies. All biochemical and biophysical parameters were estimated after 15 days of daily oral administrations of the aqueous extract.

Results: Findings showed that oral use of *C. decidua* extract (250 mg/kg) caused significant reduction in the fasting blood glucose levels in diabetic rats when compared to the control rats. Moreover, the altered level of lipid peroxidation, antioxidant, lipid profiles, liver enzymes, and also structural changes were reversed in STZ-induced diabetic rats which received *C. decidua* extract.

Conclusions: In conclusion, aqueous extract of *C. decidua* has potent antidiabetic and antioxidant activity.

Keywords: *Capparis decidua*, FTIR, Liver, Pancreas, Diabetes

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Introduction

The development of drugs from natural resources has attracted attention in pharmaceutical industries. Herbal medicines are generally considered as effective and safe with fewer side effects compared to chemical drugs.[1] One of the most important natural products of the plant species are secondary metabolites which are not essential for the growth of the organism but is responsible for their antioxidant activity. Secondary metabolites such as alkaloid, phenolic, flavonoid and terpenoid have shown promising antioxidant activities and have been used for the treatment of various diseases such as atherosclerosis, cardiovascular disease, neurological disorder, cancer and diabetes.[2,3]

Diabetes mellitus is one of the most common types of the chronic metabolic diseases which is characterized by an elevation of blood glucose levels.[4] Diabetes occurs due to insulin deficiency resulting from destruction of pancreatic β-cells by autoimmunity (type 1) and reduces insulin sensitivity of body tissues (type 2). Type 1 diabetes accounts for 5%-10% of all cases of diabetes. Chronic hyperglycemia develops complications such as neuropathy, nephropathy, retinopathy and also atherosclerosis.[5] One of the most common types of pharmaceutical therapies for the treatment of type 1 diabetes is insulin replacement via insulin pen injectors which shows several side effects in long therapy.[6] Therefore, novel approaches for the treatment and managements of diabetes mellitus are highly desirable.

Capparis decidua Edgew (Forssk.): A perennial woody plant belongs to family Capparaceae and is chiefly found in tropical and subtropical regions. This plant was traditionally used to treat several diseases. Different parts of the plant have been demonstrated to possess pharmacological properties such as antibacterial, hepatoprotective, anti-hyperlipidemic, antihypertensive and antidiabetic activities.[7] *C. decidua* contains chemical compounds such as flavonoids, steroids, phenolics, alkaloids, vitamins and many other phytochemical compounds.[8] Therefore, the present study investigated the antioxidant and antidiabetic effects of *C. decidua* on liver and pancreas of diabetic rats.

Materials and Methods

Twigs of *C. decidua* were collected from the southern east of Iran and the specimen was deposited at the herbarium of the Faculty of Science, University of Jiroft.

Preparation of the Aqueous Extract

The twigs were washed thoroughly with fresh running water, air dried under shade at room temperature and grounded into a fine powder by using grinder (Seven Star, Germany). Briefly 5 gr of powder was mixed in 100 mL of distilled water then incubated at room temperature for 4 h on rotating shaker (200 rpm). The mixture was kept in 4°C for 48 hours. The aqueous extract was filtered through Whatman No.1 filter paper and evaporated to dry using rotary evaporator

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Animals

Twenty male Wistar rats weighing 180 ± 200 g were housed under the standard conditions of 12 light/12 dark cycles, temperature 20 ± 22 °C and maintained with free access to food and water *ad libitum*. All experimental protocols used on the animals were done according to the Guiding Principles for the Care and use of Research Animals.

Induction of Diabetes with Streptozotocin

Diabetes was induced in rats by intraperitoneal (IP) injection of streptozotocin (STZ) (dissolved in 0.9% saline, pH 4.5) at a dose of 50 mg/kg body weight. After STZ injection, the rats had free access to food and water. Blood samples were taken from the tail vein 72 hours after STZ injection to measure fasting blood glucose levels. Only animals with fasting blood glucose levels (after fasting for 12 hours) over 200 mg/dL were considered diabetic and were used for further studies.[9]

Experimental Design

Rats were divided equally and randomly in four treatment groups (n=5). The control group were normal rats which received food and water *ad libitum* during the experiment. Animals in the STZ group were diabetic rats which did not receive any treatments. The STZ + C.d group were diabetic rats which were treated with aqueous extract of *C. decidua* (C.d) at a dose of 250 mg/kg. *C. decidua* extract (250 mg/kg) was administrated to the normal rats in the C.d group. At the end of the 15 days of treatments, all animals with overnight fasting were sacrificed and the blood samples were collected by cardiac puncture. The serum was collected and stored in -20°C for further biochemical assays.

Biochemical Assay

Lipid peroxidation was measured according to the method of Revin et al.[10] Catalase (CAT) activity was determined by the method of Kumburovic et al[11] and the activity of superoxide dismutase (SOD) was done according to the method of Kuyumcu and Aycan.[12] Fasting blood glucose level was measured by glucometer (Easy Gluco, Korea). Alanine transaminase (ALT), aspartate transaminase (AST), triglyceride (TG), high density lipoprotein (HDL) and low-density lipoprotein (LDL) were determined by colorimetric kits (Pars Azmoon kits).

Fourier-Transform Infrared Spectroscopy

The Fourier-transform Infrared Spectroscopy (FTIR) was used to indicate the molecular changes of liver and pancreas tissues in diabetic rats. Liver and pancreas tissue samples were washed with chilled saline, oven dried at 70°C and grounded in an agate pestle and mortar. The powdered samples were mixed with potassium bromide (KBr) and KBr pellets were made. The FTIR spectra were recorded in the range of 400-3500 cm^{-1}.

Histopathological Study

For histological examination, the livers and pancreases were removed from sacrificed rats in each group and were washed with chilled normal saline and fixed in 10% formalin. After processing with alcohol and xylene, the tissues were embedded in paraffin and sectioned into 5 µm thickness with a microtome (MicroTec, Type CUT 4050, Germany). To examine the pathological changes, all sections were stained with hematoxylin and eosin (H&E) stains.

Statistical Analysis

All data were expressed as mean ± SD. Statistical analysis were done by one-way ANOVA followed by LSD test. Differences were considered to be significant ($P<0.05$).

Results

Serum Biochemical Assay

Lipid Profiles

According to results showed in Table 1, the serum concentration of TG in diabetic rats increased significantly compared to the control rats. Moreover, the HDL level decreased in STZ-induced diabetic rats. However, when *Capparis decidua* extract was administrated in STZ rats, all these adverse effect reversed. Moreover, the LDL level did not change in all treated groups.

Effects of Capparis decidua Extract on Fasting Blood Glucose and Body Weight

Table 2 shows the results of the body weight and fasting blood glucose data. Administration of a single high dose of STZ successfully induced diabetes in animals, as evidenced by increasing mean blood glucose ($P<0.001$) at 72 hours after STZ injection. The fasting blood glucose level in the

Table 1. Effects of *Capparis decidua* Extract on Lipid Profiles of STZ-Induced Diabetic Rats (n = 5)

Group	Lipid Profiles		
	HDL (mg/dL)	LDL (mg/dL)	TG (mg/dL)
Control	46.60 ± 5.50	3.00 ± 0.00	81.00 ± 19.33
STZ	32.00 ± 4.00[b]	2.60 ± 0.54	103.80 ± 22.68[a]
STZ + C.d	46.60 ± 3.50[d]	2.60 ± 1.14	83.60 ± 2.88[c]
C.d	4.20 ± 2.68	2.70 ± 0.80	84.20 ± 7.85

Results are presented as mean ± SD. [a]$P<0.05$ and [b]$P<0.001$ represented the statistical significant between control and all treated groups. [c]$P<0.05$ and [d]$P<0.05$also showed the significant difference between STZ and diabetic group treated with *C. decidua*.

Table 2. Effect of *Capparis decidua* Extract on Fasting Blood Glucose Level and Body Weight of STZ-Induced Diabetic Rats (n = 5)

Group	Fasting Blood Glucose Level (mg/dL)		Body Weight (g)	
	3 Days	15 Days	3 Days	15 Days
Control	102.40 ± 4.72	107.33 ± 17.78	188.00 ± 7.77	213.75 ± 11.18
STZ	217.00 ± 14.83[a]	546 ± 95.75[a]	187.40 ± 9.42	156.42 ± 14.54[a]
STZ + C.d	224.00 ± 13.05[a]	165.50 ± 66.19[b]	187.80± 8.43	209.02 ± 5.05[b]
C.d	101.80 ± 2.86	107.33 ± 18.00	188.20 ± 7.49	212.08 ± 9.58

Results are presented as mean ± SD. [a] $P<0.001$ represented the statistical significant between control and all treated groups. [b] $P<0.001$ also showed the significant difference between diabetic and STZ group treated with *C. decidua*.

Table 3. Effect of *Capparis decidua* Extract on Liver Enzyme Levels of STZ-Induced Diabetic Rats (n = 5)

Group	AST (IU/L)	ALT (IU/L)
Control	135.80 ± 73.77	78.20 ± 13.89
STZ	436.00 ± 109. 85[a]	199.80 ± 71.80[a]
STZ + C.d	177.00 ± 73.71[b]	65.85 ± 11.75[b]
C.d	111.20 ± 25.22	53.25 ± 8.28

Results are presented as mean ± SD. [a] $P<0.001$ represented the statistical significant between control and STZ treated group. [a] $P<0.001$ also showed the significant difference between STZ and diabetic group treated with *C. decidua*.

STZ group was significantly higher than that in the control group at day 3. No statistically significant difference in body weight was found between the groups at day 3 day of the STZ treatment. However, when STZ treated rats received 250 mg/kg of *C. decidua* extract a decreased fasting blood glucose level was observed as compared to diabetic rats. There was a significant decrease in the body weight following the STZ treatments at 15 days. However, it was improved after the administration of *C. decidua* extract (Table 2).

Effect of Capparis decidua Extract on Liver Enzyme Activities

As shown in Table 3, serum AST and ALT activities significantly increased after the administration of STZ, as compared with the normal group ($P<0.001$). However, the levels of AST and ALT significantly decreased after the *C. decidua* treatment ($P<0.001$).

Effect of Capparis decidua Extract on Serum CAT, SOD and Lipid Peroxidation Levels

As showed in Table 4, the levels of CAT and SOD significantly decreased in the STZ treated group as compared to the normal control. However, treatment with 250 mg/kg of *C. decidua* extract significantly increased the levels of the antioxidant enzymes. Administration of STZ caused a significant increase in malondialdehyde (MDA) level as an indicator of lipid peroxidation, as compared with the normal group. However, treatment with *C. decidua* extract significantly reduced the level of serum lipid peroxidation in the STZ group (Table 4).

FTIR Spectrum Acquisition and Analysis

Figure 1 shows the FTIR spectrum acquisition and analysis of rat pancreases tissue of all treated groups in the range of 4500 to 450 cm^{-1}. The spectrum contains several bands arising from different functional groups belonging to lipid, protein, nucleic acid and carbohydrate. According to results, we focused in particular in the typical C-H stretching region of lipids at 1800 to 1000 cm^{-1} and 3000 to 2800 cm^{-1}, respectively. The absorption band and assignment of pancreas and liver tissues from the control group are presented in Table 5. The most relevant changes of pancreas tissues are obtained in the range 3000 to 2300 cm^{-1} and also1800 to 530 cm^{-1}, which belong to lipids respectively (Figure 1). The band area at 2356 missed in the pancreas of STZ-induced diabetic rats. According to the obtained results, the most changes of macromolecular structure of liver tissue was seen in the regions of 2357 (lipid region) and 1400 cm^{-1} (lipid and protein) which disappeared in diabetic group (Figure 3). Administration of *C. decidua* extract in diabetic rats appeared the peak intensities at 2357 and 1400 cm^{-1} which were belongs to macromolecular structure of lipid and protein.

Histopathology Results

The morphological features of the liver tissue from the control group showed normal hepatocyte along with central vein and normal sinusoids (Figure 3 and Table 6). In the STZ group, damaged hepatocyte, binucleated cells; an increased number of Kupffer cells, necrosis and abnormal sinusoids were observed. The administration of *C. decidua* extract in the STZ-induced diabetic rats reversed the most damage in the liver cells. Moreover, the administration of *C. decidua* extract showed a normal histological architecture of liver tissue.

Also as showed in Figure 4 and Table 7, the control rats exhibited normal histological architecture of pancreas. The

Table 4. Effect of *Capparis decidua* Extract on Antioxidant and Lipid Peroxidation Levels of STZ-Induced Diabetic Rats (n = 5)

Group	MDA (nmol of MDA/min/mg Protein)	Catalase (nmol of H_2O_2 decomposed/min/mg Protein)	SOD (I.U)
Control	0.230 ± 0.020	0.314 ± 0.023	3.218 ± 0.195
STZ	0.432 ± 0.041[c]	0.160 ± 0.023[c]	1.170 ± 0.255[c]
STZ + C.d	0.290 ± 0.059[a,d]	0.254 ± 0.043[b,d]	2.543 ± 0.337[b,d]
C.d	0.222 ± 0.031	0.331 ± 0.024	3.312 ± 0.258

Results are presented as mean ± SD. [a] $P<0.05$, [b] $P<0.01$ and [c] $P<0.001$ represented the statistical significant between control and all treated groups. [d] $P<0.001$ also showed the significant difference between STZ group and diabetic group treated with *C. decidua*

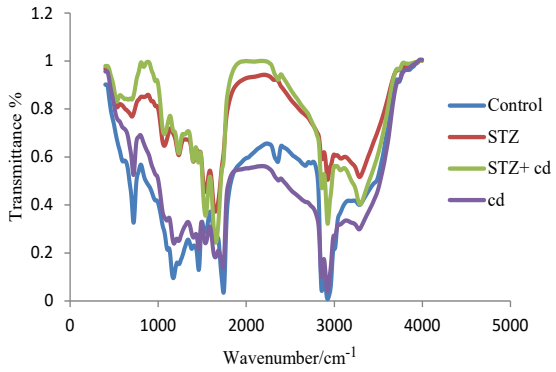

Figure 1. FTIR Spectrum of Pancreas From All Treated Rats.

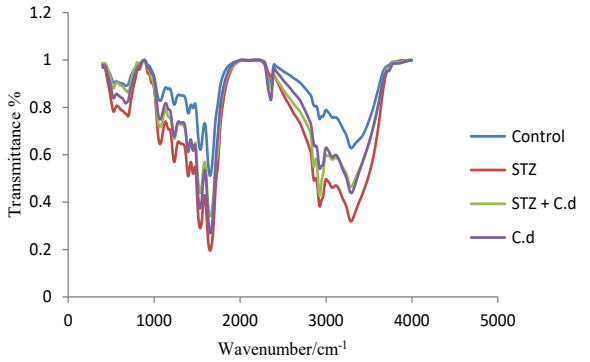

Figure 2. FTIR spectrum of Liver From All Treated Rats.

normal islet cells and pancreatic acini were found in the control group. In the STZ group, the damaged pancreatic cells with disarranged acini and islet cells observed. However, reduced β-cells and increased hyalinized islet cells were seen in the STZ group as compared to the control. The *C. decidua* extract administration decreased cell damage and increased the number of β-cells.

Discussion

In the current study, diabetes (type 1) was induced by IP injection of a single high dose (50 mg/kg) of STZ. Several studies have shown that STZ is one of the most common types of chemicals used for inducing experimental diabetes.[13,14] Due to its similarity in the structure to glucose,[15] glucose can compete with STZ, and thus, fasting animals tend to be more susceptible. For the induction of type 1 diabetes in rats, a single high dose (35-65 mg/kg) can be used.[16] The STZ transport into the β-cells through a GLUT2 transporter and its accumulation causes DNA alkylation in β-cells and finally causes cell death. In chemically induced models of type 1 diabetes, a high percentage of the endogenous beta cells are destroyed, and thus, there is little insulin production, leading to hyperglycemia and weight loss. Diabetes mellitus causes changes in the metabolism of carbohydrate, fats and protein, which resulted in hyperglycemia, hyperlipidemia and atherosclerosis.[17,18] In recent years, several reports have shown that elevated levels of oxidative stress is responsible for the development of diabetes and its complications.[19,20] Liver has an important role in lipid and glucose homeostasis. Liver abnormalities like an increased hepatic enzyme

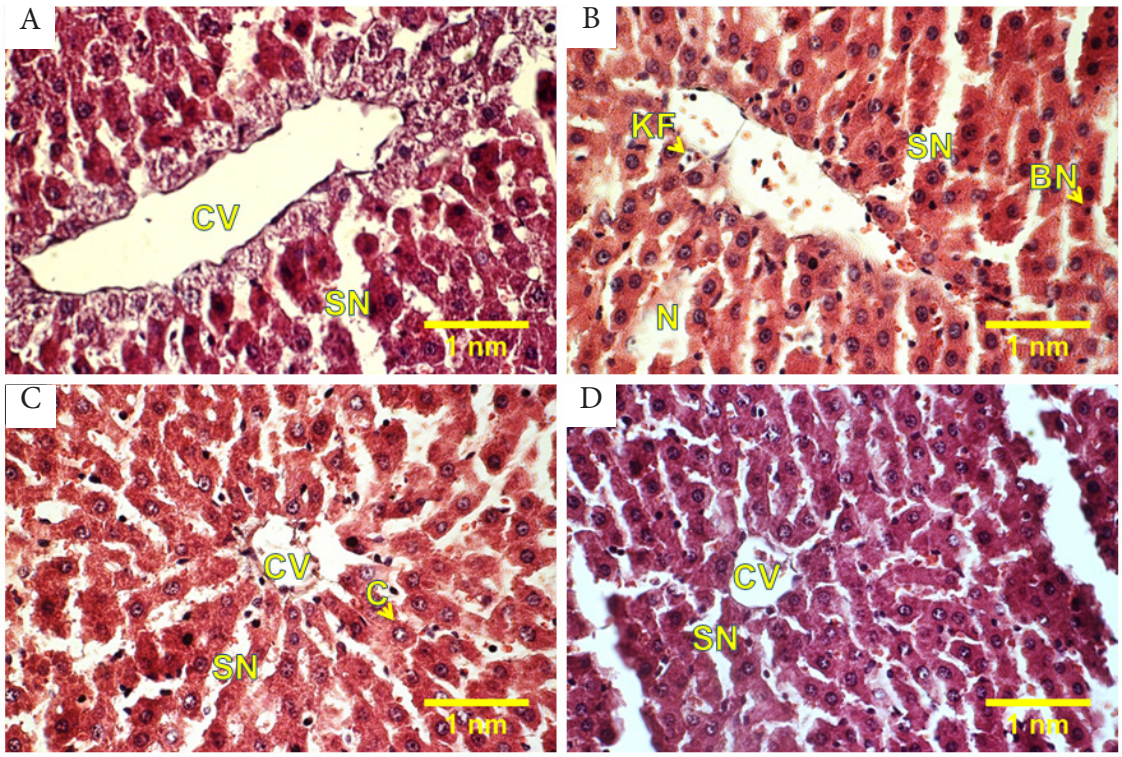

Figure 3. Effect of *Capparis decidua* on Histological Profiles of Liver From Different Treated Group. A) Control group, B) STZ treated rats, C) diabetic rats treated with 250 mg/kg *Capparis decidua* extract and D) *Capparis decidua* administrated rats. C: Hepatocyte, CV: Central vein, SN: Sinusoid, KF: Kupffer cell, BN: Binucleated cell and N: Necrosis.

Table 5. The Main Band Assignment of Pancreas and Liver Tissue From Control Group

S. No.	Wave Number (cm^{-1})		Spectral Assignment
	Pancreas	Liver	
1	3286.06	3297.50	Amide A: N-H stretching of proteins
2	2922.74	2927.85	CH_2 antisymmetric stretch: mainly lipids
3	2855.98	-	CH_2 symmetric stretch: mainly lipids
4	2357.99	2356.59	C-H stretching: mainly lipids
5	1739.14	-	Phospholipids, cholesterol esters
6	1649.67	1651.35	Amide I: protein
7	1536.98	1537.84	Amide II: proteins
8	1460.45	1451.62	CH_2 bending: mainly lipids, proteins
9	1400.06	1398.78	COO-symmetric stretch: fatty acids and amino acids
10	-	1235.22	PO^{-2}antisymmetric stretch: nucleic acids, phospholipids
11	1177.14	-	CO-O-C antisymmetric stretching: glycogen and nucleic acids
12	-	1069.75	PO^{-2}symmetric stretch: nucleic acids, phospholipids
13	719.04	-	C-O stretching: polysaccharides, glycogen
14	-	659.75, 530.80	Fingerprinting region: mainly nucleic acid

activities, abnormal fat and glycogen deposition, necrosis and hepatocyte dysfunctions is associated with diabetes.[21] In the present study, the results showed that STZ was able to increase fasting blood glucose level, liver enzyme activities (ALT and AST) and lipid peroxidation. The destruction of β-cells by STZ causes some physico-metabolic abnormalities such as body weight loss, and increase in food and water intake.[22] In the present study, a pronounce weight loss was noted in the diabetic rats but oral administration of extract was able to improve the body weight of the diabetic rats. This may be due to glucose homeostasis after treatment with the extract. The elevation of ALT and AST in the bloodstream is an indication of hepatocellular damage.[23] In STZ-induced diabetes, activation of hormone-sensitive lipase during insulin deficiency is characterized by an increased release of free fatty acids from adipose tissue which finally causes hyperlipidemia.[24] The increased triglyceride causes a decrease in the level of HDL through activating lipoprotein lipase.[25] In the present study, our experiments on lipid profiles confirm the findings of previous studies.[26,27]

Oxidative stress arises as a result of elevated levels of free radicals and impaired antioxidant defense system. The

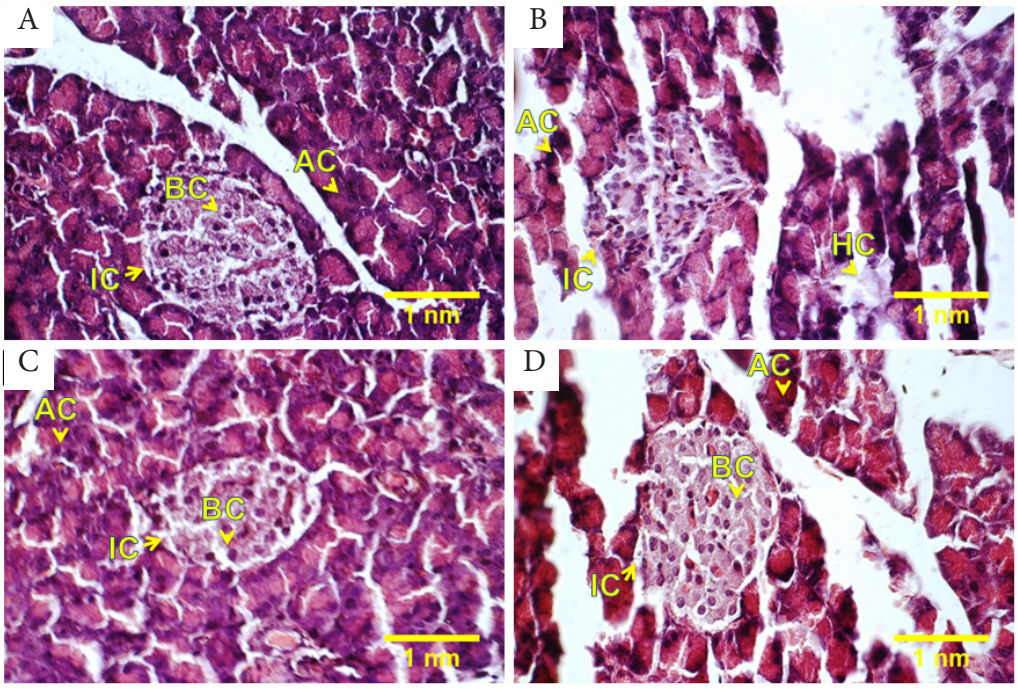

Figure 4. Histopathological Study of Effect of *Capparis decidua* on Pancreas From All Treated Rats. A) Control group, B) STZ treated rats, C) diabetic rats treated with 250 mg/kg *Capparis decidua* extract and D) *Capparis decidua* administrated rats. AC: Acini, IC: Islet cell, BC: β-cell and HC: Hyalinized islet cell.

Table 6. Histopathological Lesions in Liver From Control and Diabetic Rats Treated With *Capparis decidua*

	Control	STZ	STZ + C.d	C.d
Abnormal Sinusoid	-	+++	+	-
Necrosis	-	+++	+	-
Binucleated cell	-	++	-	-
Kupffer cell	-	+++	++	+

-: absent; +: weak, ++: moderate, +++: strong.

Table 7. Histopathological Lesions in Pancreas From Control and Diabetic Rats Treated With *Capparis decidua*

	Control	STZ	STZ + C.d	C.d
Disarranged acini	-	+++	+	-
Disarranged Islet cell	-	+++	+	-
Reduced β-cell	-	+++	++	-
Hyalinized islet cells	-	+++	++	-

-: absent; +: weak, ++: moderate, +++: strong.

STZ-induced diabetes is also characterized by an increased production of reactive oxygen species (ROS) which are involved in the etiology of several diabetic complications including hepatic damage.[25] Several studies have shown that an elevated level of glucose enhances ROS production and causes necrosis, inflammation and oxidative stress in hepatic tissues.[28,29] Nowadays, antioxidants have been extensively used to inhibit the ROS. Cappers plants contain secondary metabolites such as, alkaloids, phenols, flavonoids and glycosides. Studies have shown that polyamine alkaloid which is called spermidine is used for treating type 2 diabetes.[30,31] The antidiabetic potential of the alkaloid from the fruit of *C. decidua* in diabetic mice have been reported.[32] In accordance with our study Phenolic contains in *C. decidua* is responsible for antioxidant activities and reduced the cholesterol and triglyceride. This might be due to better insulin control in the treated group. Abdalrahman et al reported that the twigs of *C. decidua* have potent antioxidant activities.[33] Fruit extract of this plant showed a significant inhibitory effect on α-amylase and α- glucosidase, followed by flower and leave extract.[7] Based on the results, treatment of the STZ group with twigs extract of *C. decidua* significantly decreased the blood glucose and increased the antioxidant defense system activity. In another study, the administration of fruit of *Capparis aphylla* reduced lipid peroxidation in alloxan treated rats with simultaneous alteration of SOD and CAT in kidney, heart and erythrocytes.[34] The aqueous-ethanolic extract of stem of *C. decidua* demonstrated a significant reduction in ALT, AST and also hepatoprotective activity against paracetamol induced hepatotoxicity in rabbits.[35] In the present study, it was also observed that *C. decidua* administration to STZ-induced diabetic rats significantly attenuated the elevated activities of AST and ALT. This may be due to the protective effect of this extract through reversing liver and pancreas damage. The FTIR spectra have the ability to measure complex molecular vibrational modes that contain valuable information on changes occurring in various biomolecules during pathogenesis. In the present study, the structural changes of biomolecules in liver and pancreatic tissues are supported by FTIR study. Accordingly, histopathological and FTIR assays revealed that *C. decidua* was able to improve the altered lipid and protein structure of liver and pancreas and increased the β-cell of islets. These findings were consistent with other research which revealed tissue structural and functional changes in type 1 diabetes.[36] It was also reported that lower intensity of band within 1440-1390 cm^{-1} region is associated with diminished of methyl groups for enhancing pancreatic β-cell regeneration. According to the results of the present study, the band in 1400 cm^{-1} area was missing in the diabetic rats.

Conclusions

In the current study, the aqueous extract of *C. decidua* was used to evaluate its antidiabetic and antioxidant activities in STZ-induced diabetic rats. Administration of *C. decidua* extract in diabetic rats showed significant increase in antioxidant levels which was confirmed by histological and FTIR studies. Antidiabetic effects of *C. decidua* extract suggest it as a good candidate for treatment of diabetes. In conclusion, the findings of the present study showed the ability of *C. decidua* to reduce oxidative damage caused by diabetes. Additionally, this medicinal plant showed potent antidiabetic activities.

Authors' Contributions

ARG, FEG and AA contributed to the design of the study, revising the draft, and the approval of the final version of the manuscript. All authors wrote the manuscript equally.

Conflict of Interest Disclosures

The authors report no conflicts of interest.

Ethical Approval

The experimental and procedures used in this study were approved by the Ethics Committee for the Care and Use of Laboratory Animals of University of Jiroft.

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References

1. Yuan H, Ma Q, Ye L, Piao G. The traditional medicine and modern medicine from natural products. Molecules. 2016;21(5):559. doi:10.3390/molecules21050559.
2. Lietava J, Beerova N, Klymenko SV, Panghyova E, Varga I, Pechanova O. Effects of cornelian cherry on atherosclerosis and its risk factors. Oxid Med Cell Longev. 2019;2019:2515270. doi:10.1155/2019/2515270.
3. Bahmani M, Golshahi H, Saki K, Rafieian-Kopaei M, Delfan B, Mohammadi T. Medicinal plants and secondary metabolites for diabetes mellitus control. Asian Pac J Trop Dis. 2014;4 Suppl 2:S687-S692. doi:10.1016/s2222-1808(14)60708-8.
4. Tan SY, Mei Wong JL, Sim YJ, et al. Type 1 and 2 diabetes mellitus: a review on current treatment approach and gene therapy as potential intervention. Diabetes Metab Syndr. 2019;13(1):364-372. doi:10.1016/j.dsx.2018.10.008.
5. King A, Austin A. Animal models of type 1 and type 2 diabetes mellitus. In: Conn PM, ed. Animal Models for the Study of Human Disease. 2nd ed. London: Academic Press; 2017. p. 245-265. doi:10.1016/b978-0-12-809468-6.00010-3
6. McCall AL, Farhy LS. Treating type 1 diabetes: from strategies for insulin delivery to dual hormonal control. Minerva Endocrinol. 2013;38(2):145-163.
7. Zia-Ul-Haq M, Cavar S, Qayum M, Imran I, de Feo V.

Compositional studies: antioxidant and antidiabetic activities of *Capparis decidua* (Forsk.) Edgew. Int J Mol Sci. 2011;12(12):8846-8861. doi:10.3390/ijms12128846.
8. Nazar S, Hussain MA, Khan A, Muhammad G, Tahir MN. *Capparis decidua* Edgew (Forssk.): a comprehensive review of its traditional uses, phytochemistry, pharmacology and nutrapharmaceutical potential. Arab J Chem. 2020;13(1):1901-1916. doi:10.1016/j.arabjc.2018.02.007.
9. Ashraf H, Heidari R, Nejati V. Antihyperglycemic and antihyperlipidemic effects of fruit aqueous extract of *Berberis integerrima* Bge. in streptozotocin-induced diabetic rats. Iran J Pharm Res. 2014;13(4):1313-1318.
10. Revin VV, Gromova NV, Revina ES, et al. The influence of oxidative stress and natural antioxidants on morphometric parameters of red blood cells, the hemoglobin oxygen binding capacity, and the activity of antioxidant enzymes. Biomed Res Int. 2019;2019:2109269. doi:10.1155/2019/2109269.
11. Kumburovic I, Selakovic D, Juric T, et al. Antioxidant effects of *Satureja hortensis* L. attenuate the anxiogenic effect of cisplatin in rats. Oxid Med Cell Longev. 2019;2019:8307196. doi:10.1155/2019/8307196.
12. Kuyumcu F, Aycan A. Evaluation of oxidative stress levels and antioxidant enzyme activities in burst fractures. Med Sci Monit. 2018;24:225-234. doi:10.12659/msm.908312.
13. Wang-Fischer Y, Garyantes T. Improving the reliability and utility of streptozotocin-induced rat diabetic model. J Diabetes Res. 2018;2018:8054073. doi:10.1155/2018/8054073.
14. Przygodzki T, Kassassir H, Talar M, Siewiera K, Watala C. Effects of three-month streptozotocin-induced diabetes in mice on blood platelet reactivity, COX-1 expression and adhesion potential. Int J Exp Pathol. 2019;100(1):41-48. doi:10.1111/iep.12298.
15. Thangaraj P. Evaluation of anti-diabetic property on streptozotocin-induced diabetic rats. In: Pharmacological Assays of Plant-Based Natural Products. Cham: Springer; 2016. p. 145-149. doi:10.1007/978-3-319-26811-8_24.
16. King AJ. The use of animal models in diabetes research. Br J Pharmacol. 2012;166(3):877-894. doi:10.1111/j.1476-5381.2012.01911.x.
17. Katakami N. Mechanism of development of atherosclerosis and cardiovascular disease in diabetes mellitus. J Atheroscler Thromb. 2018;25(1):27-39. doi:10.5551/jat.RV17014.
18. Lazarte J, Hegele RA. Dyslipidemia management in adults with diabetes. Can J Diabetes. 2020;44(1):53-60. doi:10.1016/j.jcjd.2019.07.003.
19. Ebaid H, Bashandy SAE, Alhazza IM, Hassan I, Al-Tamimi J. Efficacy of a methanolic extract of *Adansonia digitata* leaf in alleviating hyperglycemia, hyperlipidemia, and oxidative stress of diabetic rats. Biomed Res Int. 2019;2019:2835152. doi:10.1155/2019/2835152.
20. Chatuphonprasert W, Lao-Ong T, Jarukamjorn K. Improvement of superoxide dismutase and catalase in streptozotocin-nicotinamide-induced type 2-diabetes in mice by berberine and glibenclamide. Pharm Biol. 2014;52(4):419-427. doi:10.3109/13880209.2013.839714.
21. Safhi MM, Alam MF, Sivakumar SM, Anwer T. Hepatoprotective Potential of *Sargassum muticum* against STZ-induced diabetic liver damage in wistar rats by inhibiting cytokines and the apoptosis pathway. Anal Cell Pathol (Amst). 2019;2019:7958701. doi:10.1155/2019/7958701.
22. Karigidi KO, Olaiya CO. Antidiabetic activity of corn steep liquor extract of *Curculigo pilosa* and its solvent fractions in streptozotocin-induced diabetic rats. J Tradit Complement Med. 2020;10(6):555-564. doi:10.1016/j.jtcme.2019.06.005.
23. Mansourian M, Mirzaei A, Azarmehr N, Vakilpour H, Kokhdan EP, Doustimotlagh AH. Hepatoprotective and antioxidant activity of hydroalcoholic extract of *Stachys pilifera*. Benth on acetaminophen-induced liver toxicity in male rats. Heliyon. 2019;5(12):e03029. doi:10.1016/j.heliyon.2019.e03029.
24. Hirano T. Pathophysiology of diabetic dyslipidemia. J Atheroscler Thromb. 2018;25(9):771-782. doi:10.5551/jat.RV17023.
25. Vergès B. Pathophysiology of diabetic dyslipidaemia: where are we? Diabetologia. 2015;58(5):886-899. doi:10.1007/s00125-015-3525-8.
26. Latifi E, Mohammadpour AA, Fathi B, Nourani H. Antidiabetic and antihyperlipidemic effects of ethanolic *Ferula assa-foetida* oleo-gum-resin extract in streptozotocin-induced diabetic Wistar rats. Biomed Pharmacother. 2019;110:197-202. doi:10.1016/j.biopha.2018.10.152.
27. Seedevi P, Ramu Ganesan A, Moovendhan M, et al. Anti-diabetic activity of crude polysaccharide and rhamnose-enriched polysaccharide from G. *lithophila* on streptozotocin (STZ)-induced in Wistar rats. Sci Rep. 2020;10(1):556. doi:10.1038/s41598-020-57486-w.
28. Volpe CMO, Villar-Delfino PH, Dos Anjos PMF, Nogueira-Machado JA. Cellular death, reactive oxygen species (ROS) and diabetic complications. Cell Death Dis. 2018;9(2):119. doi:10.1038/s41419-017-0135-z.
29. Oguntibeju OO. Type 2 diabetes mellitus, oxidative stress and inflammation: examining the links. Int J Physiol Pathophysiol Pharmacol. 2019;11(3):45-63.
30. Forrester SJ, Kikuchi DS, Hernandes MS, Xu Q, Griendling KK. Reactive oxygen species in metabolic and inflammatory signaling. Circ Res. 2018;122(6):877-902. doi:10.1161/circresaha.117.311401.
31. Aba PE, Asuzu IU. Mechanisms of actions of some bioactive anti-diabetic principles from phytochemicals of medicinal plants: a review. Indian J Nat Prod Resour. 2018;9(2):85-96.
32. Sharma B, Salunke R, Balomajumder C, Daniel S, Roy P. Anti-diabetic potential of alkaloid rich fraction from *Capparis decidua* on diabetic mice. J Ethnopharmacol. 2010;127(2):457-462. doi:10.1016/j.jep.2009.10.013.
33. Abdalrahman AA, El Tigani S, Yagi S. Biological activity of extracts from *Capparis decidua* L. twigs. J Med Plants Res. 2016;10(1):1-7. doi:10.5897/jmpr2015.5994.
34. Dangi KS, Mishra SN. Antioxidative and β cell regeneration effect of *Capparis aphylla* stem extract in streptozotocin induced diabetic rat. Biol Med. 2011;3(3):82-91.
35. Rehman J, Akhtar N, Asif HM, Sultana S, Ahmad M. Hepatoprotective evaluation of aqueous-ethanolic extract of *Capparis decidua* (Stems) in paracetamol induced hepatotoxicity in experimental rabbits. Pak J Pharm Sci. 2017;30(2):507-511.
36. Nurdiana S, Goh YM, Ahmad H, et al. Changes in pancreatic histology, insulin secretion and oxidative status in diabetic rats following treatment with *Ficus deltoidea* and vitexin. BMC Complement Altern Med. 2017;17(1):290. doi:10.1186/s12906-017-1762-8.