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Research Article

Clerodendrum infortunatum Attenuates Pancreatic Oxidative Stress and Dysregulated Carbohydrate Metabolism in Streptozotocin-induced Experimental Diabetes

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ABSTRACT

The prevalence of diabetes mellitus is increasing at an alarming rate and is gravely troubling human health and quality of life. Side effects of synthetic hypoglycemic agents have led to investigations on alternative sources such as herbal drugs in treating diabetes. Anti-diabetic properties of *Clerodendrum infortunatum* in streptozotocin-induced experimental diabetes were evaluated and compared with the standard anti-diabetic drug glibenclamide. Aqueous extract of *C. infortunatum* on carbohydrate metabolism revealed its hypoglycemic effect in diabetic conditions. Furthermore, it could significantly modulate insulin secretion, glycolysis, gluconeogenesis and glycogen metabolism for effective glucose homeostasis. Notably, the drug could accelerate the activities of major antioxidant enzymes and reduce the content of lipid peroxidation products in the pancreas. The study proves the efficacy of *C. infortunatum* as a potent source of phytochemicals in ameliorating diabetic complications and suggests the medicinal plant as a nutraceutical agent.

Introduction

Diabetes is one of the most widely occurring multifactorial human ailments characterized by disordered glucose metabolism and the worldwide prevalence has risen over the past two decades, leading to microvascular and macrovascular complications.[1] Obesity, change in food habits and physical inactivity are established as the risk factors for diabetes and comorbidities. According to World Health Organization (WHO) and the International Diabetes Federation, diabetes is the sixth leading cause of death worldwide and evidence suggest a predicted increase to 79.4 million diabetic patients in India by 2030.[2] Deficiency of β-cells in the endocrine pancreas and sub-sensitivity of target cells to insulin lead to high concentrations of blood glucose and other biochemical abnormalities.[3] Hyperglycaemia generates reactive oxygen species (ROS), causing cell damage and consequent secondary complications.[4,5]

Oxidative stress due to hyperglycemia causes tissue damage through multiple mechanisms such as increased flux of glucose and other sugars through the polyol pathway, increased intracellular formation of advanced glycation end products (AGEs), increased expression of the receptor for AGEs and its activating ligands,

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activation of protein kinase C isoforms, and over activity of the hexosamine pathway.[6] The resulting abnormal carbohydrate metabolism will further contribute to pancreatic β cell dysfunction.[7] Possibly due to low levels of antioxidant enzyme expressions, pancreatic β cells are more vulnerable to oxidative stress under diabetic conditions.[8] Thus the development of type 2 diabetes is usually associated with the combination of pancreatic cell dysfunction and insulin resistance.[9]The available therapy for diabetics includes insulin and various oral anti-diabetic agents, such as sulfonylureas, biguanide, thiazolidinedione, and α glucosidase inhibitors.[10] These agents, however, have restricted usage due to several undesirable side effects. Therefore, finding alternative anti-diabetes agents, especially natural ones, is desired.[11] Traditional medicinal plants have lesser adverse effects with multiple therapeutic actions due to the presence of different bioactive compounds.[12] Studies have proved that plants are exemplary sources of drugs in the treatment of diabetes.[13] Indian medicinal plants have always been a major component in the formulations of Ayurveda and Siddha medicines to successfully manage diabetes.

Clerodendrum infortunatum is a small shrub occurring throughout India's plains, traditionally used for medications. The plant is reported to have antihyperglycemic, anti-inflammatory, antimicrobial, antioxidant, anticonvulsant, analgesic, hepatoprotective, wound healing, anticancer and nootropic properties.[14] It is a common and widely used medicinal plant in Ayurveda, Homeopathy, Siddha, Unani and other traditional systems of medicine. Tribes mainly use this plant for the treatment of colic, scorpion sting, snake bite, tumors and certain skin diseases. Numerous studies have reported the free radical scavenging and antioxidant activity of various parts of CI.[15-21] Evidence shows that leaf extract of CI possesses anti-diabetic properties and the bioactive phytochemical was identified as pheophytin.[22] Furthermore, the methanolic leaf extract of CI has been reported to have remarkable preclinical antihyperglycemic activity in streptozotocin (STZ)-induced diabetic rats.[23] The extract administration improved the antioxidant status and decreased lipid peroxidation in diabetic animals. CI was also reported to have the potential to reduce testicular damage in diabetic rats.[24] CI's hypoglycemic and hepatoprotective role has already been demonstrated in STZ-induced diabetic rats.[25] Numerous studies have demonstrated the effect of various plant extracts on carbohydrate metabolism and pancreatic oxidative stress to establish the anti-diabetic potentials of medicinal plants.[26-30] Even though previous studies have shown the anti-diabetic properties of CI, the effect of CI on defective carbohydrate metabolism and pancreatic oxidative damage during diabetes has not been elucidated well.

For centuries, plants have served as a natural source of phytochemicals that aid in treatments and therapies. Plant-based pharmaceuticals help to combat life-threatening illnesses in a safe, efficient and cost-effective way. The popularity of herbal medicines is increasing day by day for pharmaceutical companies all over the world and they are constantly looking for potential bioactive compounds from medicinal plants for the development of novel anti-diabetic drugs with minimum side effects. As discussed in the previous section, CI possesses remarkable medical properties that highlight the pharmaceutical importance of the plant. Of note, CI has been used as an active ingredient in various Ayurvedic formulations such as Rasnadi ghritam, Agastya rasayana, Vathapy capsule, Bala oil, etc. Hence, in light of the aforementioned previously published articles, the present study aims to evaluate the effect of aqueous extract of CI on glucose metabolism and pancreatic oxidative stress in STZ-induced experimental diabetes. The study should facilitate to reveal the pharmacological potency of CI in diabetic conditions and can be used as an alternative solution for drugs having adverse effects. Further confirmation in clinical trials will contribute to the development of novel pharmaceuticals from CI for therapeutic intervention of diabetes.

Materials and Methods

Chemicals

Chemicals were of analytical grade and procured from Sigma Aldrich, USA and SRL Pvt. Ltd. Mumbai, India.

Plant Material and Extraction

CI whole plant was collected from Pandalam, Kerala. Its botanical identity was confirmed by Dr. Mathew Dan, Scientist E1, Plant Genetic Resource Division, Jawaharlal Nehru Tropical Botanic Garden and Research Institute. A voucher specimen (No.60694) has been deposited in JNTBGRI, Palode, Thiruvananthapuram. CI whole plant was washed, shade dried and coarse powdered. Both aqueous and hexane extract were prepared and phytochemical analysis was done. Phytochemical analysis revealed the rich composition of phytoconstituents in aqueous extract than hexane extract and hence aqueous extract of the plant (200 and 400 mg/body weight) was selected for further detailed study in experimental diabetic animal models.

Animals and Experimental Design

Male albino rats (Wistar) of body weight 200 to 250 g, were used for the study. They were provided with laboratory chow (Hindustan Lever Lab diet, India) and water *ad libitum* throughout the experimental period. The rats were housed in a room with a temperature maintained at 23 ± 1°C and 12 hours of light and dark cycles. The relative humidity of 50 ± 10% and ventilation frequency of 10 to 30 times per hour were maintained. The animals were acclimatized under laboratory conditions for two weeks before the experiments. Institutional guidelines were strictly followed throughout the study for animal experimentation and handling in conformity with the

directions given by the Government of India for the use and care of laboratory animals (Approved by Institutional Animal Ethics Committee CKL/TOX/IAEC/40-2014)

Rats were made diabetic by giving a single intraperitoneal injection of STZ (40 mg/kg body weight in 0.1M citrate buffer – pH 4.5). The animals were allowed to drink 5% glucose solution overnight to overcome the drug-induced hypoglycemia. Animals with fasting blood glucose between 200 to 250 mg/dl, three days after streptozotocin administration were considered diabetic and were selected for the study. Animals were divided into 5 groups with 6 rats each. Group I -normal rats (Vehicle control); Group II – STZ-induced diabetic rats; group III -STZ-induced diabetic rats supplemented with glibenclamide (600 µg/kg body weight); Group IV and group V –STZ-induced diabetic rats supplemented with CI water extract at the doses 200 and 400 mg/kg body weight, respectively. The experimental duration was 40 days. At the end of the experimental period, animals were sacrificed and blood and tissues were collected for further analysis.

Biochemical Parameters

Blood glucose estimation was done by the method described by Hugget and Nixon.[31] Pyruvate kinase (PK) activity assay was done by following the method described by Malcovati and Valentini[32] and hexokinase (HK) activity was estimated by the method of Crane and Sols.[33] The glycogen content was estimated by the method of Carroll *et al.*[34] phosphoglucomutase (PGM) enzyme activity was measured by the method of Najjar.[35] The method described by Sutherland estimated glycogen phosphorylase (GP) activity.[36] Catalase (CAT) activity was measured by the method of Maehly and Chance.[37] and superoxide dismutase (SOD) activity was measured by the method described by Kakkar *et al.*,[38] glutathione peroxidase (GPx) activity was estimated by the method of Agerguard and Jence,[39] glutathione Reductase (GRd) activity by the procedure of David and Richard[40], and the glutathione content (GSH) by the procedure of Patterson and Lazarow.[41] Thiobarbituric acid reactive substances (TBARS) were estimated by the method described by Okhawa *et al.*[42] Hydroperoxides (HP) and conjugated dienes (CD) were estimated by the method of John and Steven.[43] Oral glucose tolerance test (OGTT)was done according to the procedure of Nayak.[44] It was done using diabetic rats treated with 100, 200 and 400 mg of water extract of CI and it was done on the 45th day of treatment. After overnight fasting of 12 hours, the animals were administered glucose (2 g/kg body weight) and blood samples were collected from tail tip incision at 0, 30, 60, 120 and 240 minutes after glucose administration. Blood glucose was estimated by using a glucometer (Accu-check, Roche).

Histopathological Studies

The pancreas was preserved in 10% buffered formalin. The sections were stained with hematoxylin and eosin. Normal micro technique procedure was followed for microscopic preparation as described by Disbrey and Rack.[45]

Statistical Analysis

All analyses were subjected to statistical analysis using the statistical package SPSS/PC + Version 17 (SPSS Inc, Chicago, IL, USA). Data were analyzed by one-way analysis of variance (ANOVA). All the results were expressed as mean value ± SD. Duncan's multiple range test made pair-fed comparison between the groups. *p-values* of 0.05 or less were considered significant.

Results and Discussion

Diabetes mellitus (DM) is a heterogeneous metabolic disorder characterized by hyperglycemia with derangement of carbohydrate metabolism resulting from defective insulin secretion, insulin action, or both. Increased free radical generation and oxidative stress are hypothesized to play an important role in the pathogenesis of diabetes and its late complications. Pancreatic beta cells are among the most metabolically active tissues within the human body, and they are highly dependent on oxidative metabolism and elevated glucose concentrations.[46,47] Thus the altered metabolic function along with abnormal pancreatic oxidative stress, will further complicate diabetes-associated pathologies. Over the past decade, the use of complementary and alternative medicines for the management of diabetes has greatly increased around the world. Hence the present study evaluated the effect of an aqueous extract of CI on carbohydrate and oxidative metabolism in experimental diabetic animals.

Blood Glucose and Glycolytic Enzymes Level

In diabetes, tissue does not utilize blood glucose, resulting in hyperglycemia through pancreatic burnout and insulin resistance.[48] The decreased levels of PK and HK result in diminished utilization of glucose and increased amounts of blood glucose.[49] Increased activity of HK and PK results in the activation of glycolysis, leading to greater glucose uptake from the blood by the liver cells and an increase in the utilization of glucose for energy production. In agreement with these reports, STZ-induced diabetic rats in the present study also showed significantly high glucose levels. Likewise, the glycolytic enzyme activities decreased in diabetic rats when compared to normal rats. Administration of an aqueous extract of CI at a dose of 400 mg/kg body weight and glibenclamide significantly reduced the blood glucose level (Fig. 1) and increased the activity of glycolytic enzymes (Table 1). The observed beneficial effects of CI in modulating glucose levels and glycolytic enzyme activities clearly establish the hypoglycemic potential of CI in experimental diabetes.

Table 1: Activity of pyruvate kinase and hexokinase

Groups	*Pyruvate kinase (U/mg protein)*	*Hexo kinase(U/mg protein)*
Group I	17.18 ± 1.67[a]	1.93 ± 0.17[a]
Group II	2.81 ± 0.26[b]	0.93 ± 0.06[b]
Group III	10.18 ± 0.93[c]	1.52 ± 0.13[c]
Group IV	4.52 ± 0.37[d]	1.11 ± 0.09[d]
Group V	8.57 ± 0.79[e]	1.42 ± 0.12[e]

Results are expressed as mean ± SD Values with same superscript do not differ significantly. Significance accepted at $p < 0.05$

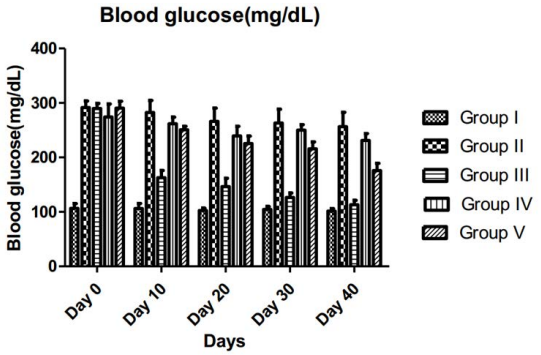

Fig. 1: Serum glucose level. Results are expressed as mean ± SD.

Glycogen Content and Glycogen Metabolism Enzyme Activities

Glycogen is mainly stored in the liver and muscles as stored form of glucose and provides the body with a readily available source of energy if blood glucose levels decrease.[50] The rate of glycogen synthesis is impaired in type 2 diabetes and evidence shows that in diabetic conditions, the glycogen content is low in the liver and skeletal muscle, which can be due to the excessive breakdown of glycogen.[51] Also, due to diminished insulin secretion, excess blood glucose can't be stored as glycogen by the liver and skeletal muscles. The activity of glycogen synthase (GS), the rate-limiting enzyme for glycogen synthesis, is reduced in type 2 diabetes.[52,53] Consistent with these reports, the results from present study also showed a dysregulated glycogen metabolism in diabetic rats. Administration of water extract of CI (400 mg/kg body weight) and glibenclamide significantly increased the hepatic and muscle glycogen content compared to diabetic rats (Table 2). Glycogen phosphorylase (GP) and phosphoglucomutase (PGM) are important enzymes in glycogen metabolism. GP catalyzes the rate-limiting step in glycogenolysis in animals by releasing glucose-1-phosphate from the terminal alpha-1,4-glycosidic bond. GP is regulated by both allosteric control and phosphorylation.[54] PGM is a highly polymorphic enzyme that plays a key role in glycogen metabolism. The decreased glycogen content with increased GP and decreased PGM results in diabetic conditions. The results of the present study are in line with these reports. Administration of CI and glibenclamide significantly decreased the activity of GP and increased the activity of PGM in treated diabetic rats (Table 3). These results explore the role of aqueous extract of CI in the regulation of glycogen metabolism.

Table 2: Glycogen content

Groups	*Skeletal muscle (mg/g tissue)*	*Liver (mg/g tissue)*
Group I	42.13 ± 3.91[a]	9.53 ± 0.81[a]
Group II	11.78 ± 1.31[b]	1.88 ± 0.09[b]
Group III	36.15 ± 3.32[c]	7.13 ± 0.61[c]
Group IV	20.56 ± 1.88[d]	3.15 ± 0.26[d]
Group V	29.17 ± 2.53[e]	5.93 ± 0.52[e]

Results are expressed as mean ± SD Values with same superscript do not differ significantly. Significance accepted at $p < 0.05$

Oral Glucose Tolerance Test

Oral glucose loading raises blood glucose levels temporarily without damaging the pancreas. Hence, the therapeutic potential of the extract in the management of diabetes can be demonstrated by its blood glucose-lowering efficacy on orally glucose-loaded mice. In the present study oral glucose tolerance test was conducted, using diabetic rats treated with 100, 200 and 400 mg/body weight of water extract of CI, to confirm the hypoglycemic effect of CI. It was found that CI (400 mg/kg body weight) could significantly control the blood glucose level in GTT. The maximum reduction was observed in 240 min (Fig. 2).

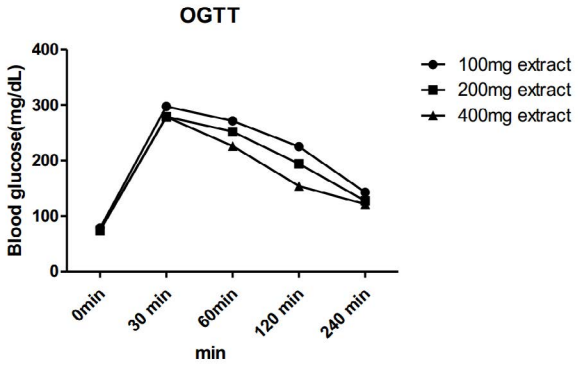

Fig. 2: Oral glucose tolerance test. Results are expressed as mean ± SD

Table 3: Activities of glycogen phosphorylase and phosphoglucomutase

Groups	*Glycogenphosphorylase (U/mg protein)*	*Phosphoglucomutase (U/mg protein)*
Group I	128.13 ± 11.92[a]	9.95 ± 0.93[a]
Group II	221.56 ± 19.91[b]	1.12 ± 0.09[b]
Group III	156.52 ± 14.88[c]	7.91 ± 0.73[c]
Group IV	195.69 ± 19.13[d]	3.78 ± 0.33[d]
Group V	175.77 ± 17.07[e]	5.83 ± 0.54[e]

Results are expressed as mean ± SD Values with same superscript do not differ significantly. Significance accepted at $p<0.05$

Insulin Levels

Insulin is a key player in the control of intermediary metabolism and it has profound effects on both carbohydrate and lipid metabolism. Consequently, derangements in insulin signalling have devastating effects on many organs and tissues that will ultimately result in various metabolic abnormalities.[55] Glucose is the primary physiological stimulus for the regulation of insulin synthesis in the pancreatic β cells.[56] In the present study, the level of insulin was significantly low in diabetic rats compared to normal rats. Supplementation of glibenclamide and aqueous extract of CI could significantly increase the level of insulin in the treated group when compared to the diabetic group. This shows the stimulatory effect of CI on insulin production by the pancreas and supports previous findings of the effect of CI on glucose and glycogen metabolism (Table 4).[57,58]

Activities of Gluconeogenic Enzymes

Fructose-1,6-bis phosphatase (F-1,6-BP) and glucose-6-phosphatase (G-6-P) are regulatory enzymes of the gluconeogenic pathway. G-6-P regulates the final step of glucose production in the liver and kidney by catalysing the dephosphorylation of glucose 6 phosphate to free glucose.[59] F-1,6-BP catalyses the dephosphorylation of fructose 1,6 bis phosphate to fructose-6-phosphate.[60] The activities of these enzymes increase in diabetic conditions resulting in a decrease in glycolytic flux.[61] The results from the present study are in agreement with this factor. While oral administration of aqueous extract of CI at a dose of 400 mg/kg body weight and glibenclamide significantly decreased the activity of F-1,6-BP and G-6-P in treated diabetics (Table 5). These results clearly highlight the effect of CI on the activities of gluconeogenic enzymes.

Pancreatic Antioxidant Enzyme Activities and Reduced Glutathione Content

Oxidative stress, caused by a relative overproduction of reactive oxygen species (ROS), plays a key role in the pathogenesis of late diabetic complications.[62] In addition to an increase in ROS, a decrease in antioxidant enzyme activities occurs in diabetes mellitus. The present results were in line with these reports. Activities of major antioxidant enzymes like CAT, SOD, GPx, GST and GRd were significantly decreased in the pancreas of diabetic rats when compared to normal. Administration of CI and glibenclamide significantly increased the activities of antioxidant enzymes (Table 6). GSH is a major endogenous antioxidant that counteracts free radical-mediated damage. In the present study, GSH level in the pancreas was decreased significantly in diabetic rats. However, the administration of 400 mg aqueous extract of CI and glibenclamide increased the GSH levels (Table 6). This indicates the antioxidant protection offered by CI in diabetic conditions which is in concordance with previous reports.[63]

Table 4: Insulin level

Groups	*Plasma insulin (µIU/ml)*
Group I	3.37 ± 0.56 [a]
Group II	0.20 ± 0.08 [b]
Group III	2.95 ± 0.58 [c]
Group IV	0.85 ± 0.24 [d]
Group V	2.15 ± 0.39 [e]

Results are expressed as mean ± SD Values with same superscript do not differ significantly. Significance accepted at p<0.05

Table 5: Activities of gluconeogenic enzymes

Groups	*Fructose-1,6-bisphosphatase (U/mg protein)*	*Glucose-6-phosphatase (U/mg protein)*
Group I	17.12 ± 1.69[a]	158.13 ± 15.12[a]
Group II	28.17 ± 2.32[b]	228.53 ± 21.53[b]
Group III	20.15 ± 1.93[c]	178.15 ± 17.15[c]
Group IV	25.73 ± 2.48[d]	203.56 ± 19.98[d]
Group V	22.59 ± 2.11[e]	188.72 ± 18.23[e]

Results are expressed as mean ± SD Values with same superscript do not differ significantly. Significance accepted at p < 0.05

Pancreatic Lipid Peroxidation Products Concentration

Free radicals derived from oxygen have been implicated in the pathophysiology of various diseases including diabetes mellitus. Because of their highly unstable nature, free radicals are difficult to measure directly. So levels of various lipid peroxidation products have been used as an indicator of free radical activity. The dysregulation of antioxidant defences during diabetes may lead to disruption of cellular function, cause oxidative damage to membranes and enhance susceptibility to lipid peroxidation. Auto oxidation of glucose can also promote free radical formation in diabetes.[64] Damage of enzymes and increased insulin resistance, resulting from the free radical formation in diabetes, may further lead to non-enzymatic glycation of proteins, glucose oxidation and increased lipid peroxidation.[65] The increased concentration of lipid peroxidation products and increase in oxygen free radicals could be due to their increased production or decreased destruction.[66] In line with these reports, in the present study,the concentration of lipid peroxidation products such as TBARS, HP and CD were significantly elevated in the pancreas of the diabetic group when compared to the normal group (Table 7). However, the treatment with CI (400 mg/kg body weight) and glibenclamide significantly reduced the concentration of lipid peroxidation products compared to the diabetic rats. Thus, CI could effectively protect the pancreas from oxidative damage induced by diabetic stress signalling.

Histopathological Analysis of the Pancreas

During diabetes, the pancreatic islets show various histology abnormalities that reflect their functional

Table 6: Activities of antioxidant enzymes in pancreas

Groups	*CAT*	*SOD*	*GRd*	*GPx*	*GSH*
Group I	13.15 ± 0.98[a]	27.15 ± 1.92[a]	22.53 ± 2.01[a]	28.52 ± 2.23[a]	310 ± 27[a]
Group II	5.34 ± 0.47[b]	8.23 ± 0.72[b]	9.52 ± 0.85[b]	11.43 ± 0.95[b]	99 ± 8.7[b]
Group III	7.11 ± 0.68[c]	15.15 ± 1.10[c]	12.73 ± 1.02[c]	16.74 ± 1.32[c]	143 ± 13.52[c]
Group IV	8.07 ± 0.75[d]	17.77 ± 1.30[d]	15.77 ± 1.14[d]	19.53 ± 1.59[d]	175 ± 15.43[d]
Group V	9.92 ± 0.93[e]	22.16 ± 1.98[e]	18.99 ± 1.29[e]	23.43 ± 2.04[e]	249 ± 19.72[e]

Results are expressed as mean ± SD Values with same superscript do not differ significantly. Significance accepted at $p < 0.05$

Table 7: Activities of lipid peroxidation products in pancreas

Groups	*TBARS (mM/100 g tissue)*	*HP (mM/100 g tissue)*	*CD (mM/100 g tissue)*
Group I	0.72 ± 0.06[a]	112.53 ± 10.77[a]	27.52 ± 2.23[a]
Group II	3.15 ± 0.22[b]	215.00 ± 19.43[b]	67.00 ± 5.99[b]
Group III	2.42 ± 0.19[c]	174.52 ± 15.92[c]	51.12 ± 5.11[c]
Group IV	2.19 ± 0.17[d]	161.74 ± 14.93[d]	43.47 ± 3.98[d]
Group V	1.98 ± 0.11[e]	142.00 ± 13.74[e]	37.19 ± 2.93[e]

Results are expressed as mean ± SD Values with same superscript do not differ significantly. Significance accepted at $p<0.05$

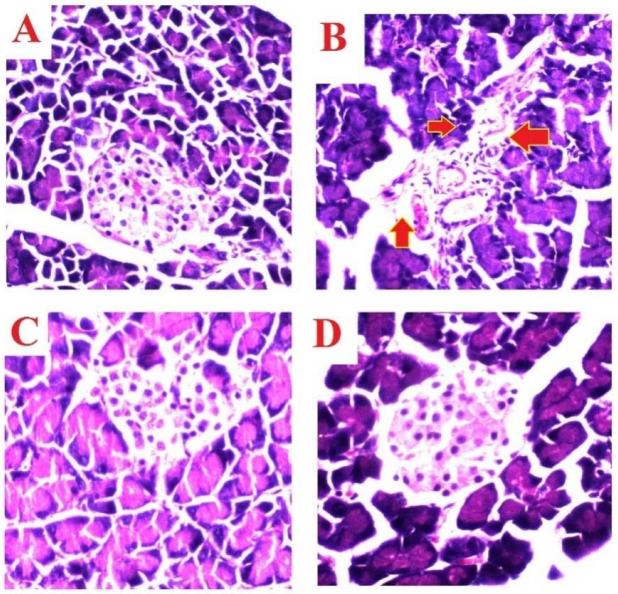

Fig. 3: Histopathological analysis of pancreas. Six experiments were performed and that the given pictures are a representative of these experiments. Photomicrograph of pancreas stained with hematoxylin–eosin. (A) Normal rats: Normal histology of pancreas. Healthy Islets of Langerhans with more number of β cells.(B). Streptozotocin induced diabetic rats: Islets of Langerhans lost it's normal architecture. Inflammatory and necrotic changes are observed in β cells. (C) Diabetic rats given glibenclamide (600 µg/kg): Near normal histology of pancreas with moderate number of β cells. Inflammatory and necrotic changes were significantly reduced in β cells. (D) Diabetic rats given 400 mg/ kg water extract of CI: Near normal histology of pancreas with moderate number of β cells. Inflammatory and necrotic changes were significantly reduced in β cells.

irregularities. Studies have shown that diabetes will cause the destruction of pancreatic islets that results in a reduction in the number of β cells.[67,68] In addition, evidence shows that STZ administration can induce pancreatic β-cell destruction in rats that leads to defective insulin secretion.[69,70] In accordance with these studies, in the present study, the pancreas of STZ-induced diabetic rats lost its normal architecture of islets of langerhans with less number of β cells. Inflammatory and necrotic changes were also observed in β cells of diabetic rats. In contrast, the pancreas of normal rats showed healthy islets of langerhans with more β cells. The pancreas of glibenclamide and CI-treated rats showed near-normal histology of the pancreas with a moderate number of β cells. The inflammatory and necrotic changes were significantly reduced in β cells of drug-treated rats. The results are shown in Fig. 3.

Hence, the present study's results demonstrate CI's anti-diabetic properties and explore its effect on carbohydrate metabolism and pancreatic oxidative status. The overall effect was comparable with the glibenclamide-treated group. The observed beneficial effects can be due to the synergistic effect of various phytochemicals in the extract. Detailed studies are warranted to elucidate CI's detailed cellular and molecular mechanism of action on diabetic stress signaling pathways. The findings may help to develop potential pharmaceutical formulations that can prevent the progression of various diabetic complications.

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Conflict of Interest

The authors declare that they have no conflicts of interest to disclose.

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