

Research Article

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Unveiling the anti-diabetic potential of *Clerodendrum splendens* leaf extract in STZ and high-fat diet-induced type 2 diabetic rats

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ABSTRACT

Background: Type-2 Diabetes Mellitus is a chronic and rising illness worldwide and natural anti-diabetic agents may be attractive alternatives to modern anti-diabetic drugs. **Objective:** This research looked into the anti-diabetic properties of *Clerodendrum splendens* (CS) leaf extract in type-2 diabetic rats. **Methods:** Glucose tolerance was tested orally (OGTT) in normal animals. Type-2 diabetes was mediated with high fat diet and a single IP injection of streptozotocin and diabetic rats with FBG level of 8–12 mmol/L were used in the study. Body weight and serum glucose were determined at every 7 days for 28 days. After 28 days, weight of pancreas, serum lipid profile, kidney & liver markers, HbA1C & liver glycogen contents were estimated. *In-vitro* α -amylase inhibitory assay, glucose utilization capacity, remaining sucrose content in the gut and gut motility were tested. **Results:** *C. splendens* showed significant effect in acute ($p<0.001$) and sub-chronic ($p<0.001$) hypoglycemic study. It slightly inhibited α -amylase ($IC_{50}=2.29$ mg/mL), significantly increased glucose utilization ($p<0.01$), retained gut sucrose ($p<0.01$) and inhibited GI motility ($p<0.01$). The extract also improved lipidemic status ($p<0.01$); creatinine ($p<0.01$), urea ($p<0.05$); enhanced liver glycogen storage ($p<0.05$) and reduced SGPT ($p<0.01$) & SGOT ($p<0.001$). **Conclusion:** *C. splendens* exhibited anti-diabetic potential by reducing carbohydrate absorption, increasing peripheral glucose utilization. It also improved lipids and other biochemicals linked to type-2 diabetes mellitus.

Keywords: Diabetes Mellitus, *C. Splendens*, A-Amylase, Glucose Utilization Capacity, Residual Gut Sucrose.

INTRODUCTION

Diabetes mellitus, commonly referred to as diabetes, is a long-term metabolic illness that occurs when the body is not able to make enough insulin or use it efficiently, which results in elevated blood glucose levels. Uncontrolled chronic hyperglycemia can harm many body organs and result in life-threatening health issues like cardiovascular disease, neuropathy, nephropathy, and eye illness (retinopathy and blindness) [1]. One of the top four non-communicable diseases (NCDs) is diabetes mellitus, a significant public health issue. The last several decades have seen a rise in both the number of cases and the prevalence of diabetes [2]. Diabetes has reached concerning proportions and is one of the 21st century's fastest-growing worldwide health concerns. Currently, it is thought to affect 589 million adults globally, and is predicted to rise to 853 million (1 in 8 adults) by 2050. Furthermore, it is estimated that 4 in 10 are unaware that they have the condition of type-2 diabetes [1,3].

Biguanides and sulphonylureas are examples of oral anti-hyperglycemic medications that are essential for the treatment of diabetes; nevertheless, these medications might have adverse effects like hypoglycemia, weight gain, GI upset etc [4]. Many researchers have verified the benefits of medicinal plants with hypoglycemic effects, and the majority of people in Bangladesh, particularly in rural areas, use herbal medicines to treat their diabetes. So, these plant-based anti-diabetic treatments have the potential to both repair metabolic imbalances and postpone the onset of diabetic complications leading to the interest of searching for a safer and cost-effective alternative skipping the adverse effects of modern anti-diabetic agents [5].

C. splendens (CS) of Lamiaceae family (formerly under Verbenaceae family), also known as bleeding heart vine, is an ascending evergreen shrub with eye-catching red blossoms [6,7].

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It is endogenous to Western Africa and is most frequently distributed in Asia (Bangladesh), west and central Africa (Senegal, Angola and Congo) [8]. It is a shrub that grows up to 2-5 m high, with leaves up to 18 cm long and 12 cm broad; the flowers are scarlet and borne in many-flowered clusters [7]. Phytochemical analysis of *C. splendens* leaves revealed the presence of steroids, triterpenes, alkaloid, flavonoids, glycosides, carbohydrates and tannins [9]. In phytomedicine, the plant has been utilized to manage injuries and cure illnesses. It is used as sedative, analgesic, cardio-protective, anti-inflammatory, oxytocic, antispasmodic and immune modulators. The plant is also used in yellow fever, panacea of witchcraft, malaria, coughs, buboes, venereal infections (gonorrhea and syphilis), skin diseases, ulcers, rheumatism, asthma, diarrhoea, dysentery, haemorrhoids, menstrual cycle troubles and uterine fibroid [6, 10-12]. The current investigation was carried out to examine the anti-diabetic efficacy of the *C. splendens* leaves extract in STZ generated type-2 diabetic rat model.

MATERIAL AND METHODS

Collection of plant and extract preparation

Leaves of *C. splendens* were collected from Dhamrai area, identified and authenticated from the Bangladesh National Herbarium, Mirpur, Dhaka and the herbarium specimen was deposited (specimen number: DACB 41180). After a thorough washing and drying at 35 °C to 40 °C, the collected materials were ground into an extractable powder. Ethanol was used to extract the powder using Soxhlet extraction method. Finally, the extract was subjected to drying and a solid mass was preserved for further experiments.

Experimental animals

Swiss Albino mice (25–30 g) and Sprague Dawley rats (180–200 g) of both sexes, were gathered from the animal research lab of Pharmacy Department at Jahangirnagar University in Savar, Dhaka for the experiments. Experimental animals were maintained under conventional circumstances (temperature of 27.0±1.0°C, RH: 55–65% and 12/12-h light/dark cycle). Additionally, they had unfettered access to food and drink. Before the studies began, the animals were given a week to get used to the laboratory environment. Approval was taken from the animal ethical committee of the Jahangirnagar University to conduct all animal experiments (Ref No.: BBEC, JU/M 2018 (12)2).

Toxicity studies

An acute oral toxicity analysis of the plant extract was conducted using Swiss Albino mice weighing 25–30g, regardless of sex. The extract was proven to be safe up to 5000 mg/kg (p.o.) [13].

Experimental Induction of diabetes

Continuous administration of animal fat for 60 days and a single IP dose of Streptozotocin (STZ) (40 mg/kg b.w.) caused rats to develop type-2 diabetes and after seven days of receiving STZ injection, diabetic rats that had blood glucose levels between 8 and 12 mmol/L during fasting were chosen for the experiment [14,15].

Oral glucose tolerance test (OGTT) in type-2 diabetic rats

Overnight fasted rats with type-2 diabetes were allocated into control group, standard (glibenclamide 10 mg/kg) and test groups (CS 250 mg/kg & CS 500 mg/kg). In each group, a glucose solution (3.0 g/kg) was given orally after 30 min of extract administration. Following 0, 60, and 120 min of glucose administration, a sample of blood was extracted from the vein of tail and the glucose levels were determined [16,17].

Sub-chronic hypoglycemic study

Twenty-four hyperglycaemic (type-2) rats were divided into group II to group V except group-I (n=6). Non-diabetic rats were selected in group-I and were treated with DW (10 mL/kg b.w.; normal control), group II served as untreated diabetic group, group III as STD (glibenclamide, 10 mg/kg b.w.) and group IV & V were fed with *C. splendens* (250 & 500 mg/kg b.w.) extract respectively. Every dose was continued for 28 days in hyperglycaemic rats. Body weight and fasting serum glucose levels were determined at every 7 days for 28 days. In the end, sacrifice of animals was done following anaesthesia applying ketamine (IP); blood was collected and subjected to biochemical analysis. Organs were isolated and weighed out [14,15].

Alpha-amylase inhibitory assay

250 µL of extract (0.125–2 mg/mL) was kept in a test tube and solution of α-amylase (250 µL) was mixed and maintained (10 min). Then 250 µL of 1% starch solution was mixed and incubated for 10 min. Addition of DNSA terminated the reaction and the test tubes were then kept in boiling water (5 min) and cooled; distilled water was used to dilute the solution before recording the absorbance at 540 nm. Acarbose (0.125-2 mg/mL) was used as standard [18]. The α-amylase inhibitory potential was calculated and IC₅₀ was determined.

Assessment of in-vitro glucose utilization capacity by isolated rat diaphragm

Twenty-four normal rats (180 to 200 g), fasted for 12 h were divided into distinct groups (n=6) & used in this experiment. Different groups were treated with respective treatment accordingly. Rats were sacrificed; diaphragms were dissected out and maintained in the test tube at 37 °C for 30 min with shaking (140 cycles/min). Glucose uptake per gram of diaphragm was calculated [19,20].

Estimation of residual gut sucrose content

After 12 h of fasting, normal rats were given the test extract or an equivalent volume of water orally, along with a 50% sucrose solution, as test and control groups, respectively. The gastrointestinal system was removed and divided into six sections: the stomach, the upper 20 cm, middle and lower 20 cm of the small intestine, the caecum and the large intestine. Centrifuge of each segment was continued for 10 min (3000 rpm) after washing with ice-cold saline of acidic pH. After being pipetted out, the supernatant was heated in sulfuric acid for two h. The amount of released glucose was used to compute the GI sucrose content [15, 21].

Gastrointestinal motility test with BaSO₄ milk

24 fasted mice distributed into distinct groups (n=6) were given vehicle, loperamide and test extract at 250 mg/kg and 500 mg/kg, respectively. After 30 min, 15% BaSO₄ was provided to each mouse and after 30 min of BaSO₄, mice were sacrificed. The quantification of traversed distance by BaSO₄ was done and represented as the percentage of the overall length of small intestine [22].

Estimation of liver glycogen content

The anthrone method was employed to investigate the stored content of glycogen inside the rat liver [23].

Statistical analysis

Data arrangement, % inhibition determination and preparation of graphs employed MS Excel (2007). Data from animal experiments were statistically analyzed by ANOVA (one way) following Bonferroni's or Dunnett's post hoc test applying SPSS 16.0. Presentation of data followed Mean±SEM. The results were statistically considered as significant when $p < 0.05$ (*), $p < 0.01$ (**) & $p < 0.001$ (***) as compared to the disease subjects as well as when

$p < 0.05$ (†), $p < 0.01$ (††) & $p < 0.001$ (†††) as compared to the normal subjects [15].

RESULTS

The investigation of acute toxicity revealed the plant as nontoxic. There was no lethality, toxic responses or changes in behavior found by *C. splendens* extract 5g/kg bw dose for a period of 72 h observation.

In terms of the tolerance test of glucose via oral route (OGTT) in type-2 rats (figure 1), the pretreatment or baseline showed almost same glucose level. At 60 min of glucose load, CS demonstrated no significant effect. However, following 120 min, CS showed insignificant glucose tolerance at 250 mg/kg dose whereas improved glucose tolerance significantly ($p < 0.001$) at 500 mg/kg while compared to the vehicle treated diabetic control.

From the 28 days examination in type 2 diabetic rats generated by STZ (figure 2), at day 0 to day 14 depicted no notable changes in glucose level by CS extract. At day 21, CS extract at 250 as well as at 500 mg/kg diminished glucose level significantly ($p < 0.001$). At day 28, the extract declined the glucose concentration significantly at 250 mg/kg ($p < 0.01$) as well as at 500 mg/kg ($p < 0.001$). Therefore, sub-chronic hypoglycemic study indicated the glucose lowering efficacy of the CS extract in type-2 animals. Treatment with *C. splendens* at 250 mg/kg could not significantly decrease the HbA1C level whereas at 500 mg/kg, it declined the HbA1C concentration significantly ($p < 0.05$) when contrasted with the diabetic group (figure 3).

The CS extract inhibited the α -amylase enzyme showing IC_{50} value of 2.29 mg/mL (figure 4). Acarbose (reference drug) displayed the maximum potential for the inhibition (90.65%) with the IC_{50} value of 0.42 mg/mL.

Impact of the CS extract on the glucose utilization capacity by isolated rat diaphragm described that insulin significantly ($p < 0.05$) enhanced the glucose uptake by diaphragm. CS extract alone insignificantly but treatment with CS extract along with insulin enhanced the glucose uptake significantly ($p < 0.01$) against the untreated animals (figure 5).

The test extract resulted in an insignificant retention of sucrose from stomach, upper & middle small intestine and large intestine as

compared to the respective control group. The CS extract was able to retard the absorption significantly ($p < 0.01$) at 240 min from lower small intestine whereas it was significant at 120 ($p < 0.05$) & 240 min ($p < 0.01$) from the ceacum (figure 6).

Ethanollic CS extract at 250 mg/kg insignificantly reduced GI motility but at 500 mg/kg, inhibited the motility significantly ($p < 0.01$) when calculated with the control animals (figure 7).

As the most common complications of hyperglycemia, the untreated type-2 animals significantly increased serum lipids (figure 8). After a 28 days treatment, CS extract at 250 mg/kg significantly reduced the hike of TC ($p < 0.01$), LDL-C ($p < 0.001$) & increased HDL-C ($p < 0.05$) with no significant effect on TG. At 500mg/kg, CS significantly declined the level of TC ($p < 0.001$), TG ($p < 0.001$) & LDL-C levels ($p < 0.01$) and progressed HDL-C level ($p < 0.01$) when calculated against disease control animals.

Oral treatment with CS extract at 250 mg/kg reduced the SGPT level insignificantly which was significant ($p < 0.01$) at 500 mg/kg dose. The extract significantly reduced the SGOT level at 250 mg/kg ($p < 0.01$) as well as at 500 mg/kg ($p < 0.001$) while analyzed with the diabetic control population (figure 9). Sub-chronic treatment of CS extract at 250 mg/kg did not significantly reduce creatinine and blood urea level whereas at 500 mg/kg CS significantly lowered the creatinine level ($p < 0.01$) and concentration of blood urea ($p < 0.05$) in animals suffering from type-2 diabetes (figure 9) against the respective control animals (figure 9).

The content of glycogen in the liver of diabetic rats was dropped sharply in contrast to normal animals (figure 10). Administration of CS extract at 250 mg/kg insignificantly enhanced the storage of liver glycogen. At 500 mg/kg, CS increased the storage of liver glycogen level significantly ($p < 0.05$) as compared to the corresponding control subjects.

STZ caused the loss of body weight and organ weight in the hyperglycemic animals when considered with normal animals. After the 28 days treatment, CS extract could increase the body weight insignificantly as compared to the diabetic animals (figure 11). The injurious effect of STZ damaged the pancreas health. CS extract at 250 mg/kg ameliorated the pancreas health insignificantly while it was significant ($p < 0.001$) at 500 mg/kg when contrasted to the diabetic rats (figure 11).

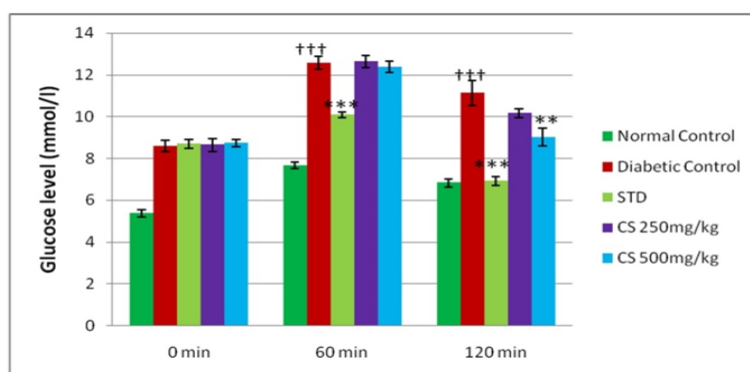


Figure 1: Potential of *C. splendens* (CS) on the glucose loaded type-2 diabetic rats (OGTT)

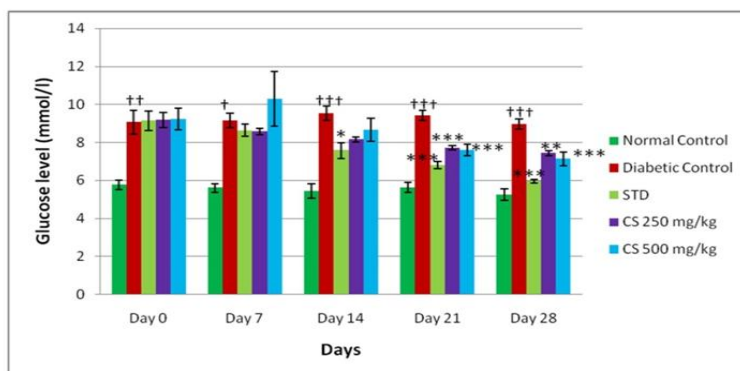


Figure 2: Potential of *C. splendens* (CS) to lower fasting blood glucose level

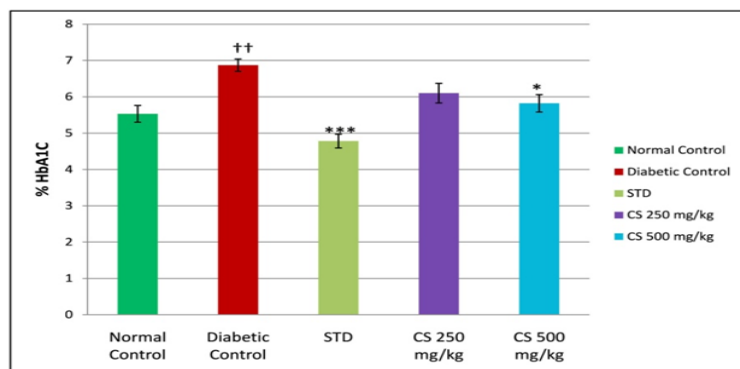


Figure 3: Effect of *C. splendens* (CS) on the % glycosylated haemoglobin (HbA1C) level

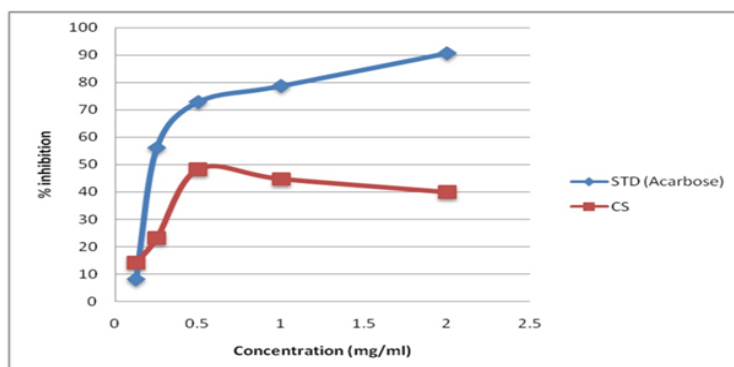


Figure 4: Effect of *C. splendens* on the α -amylase inhibitory assay

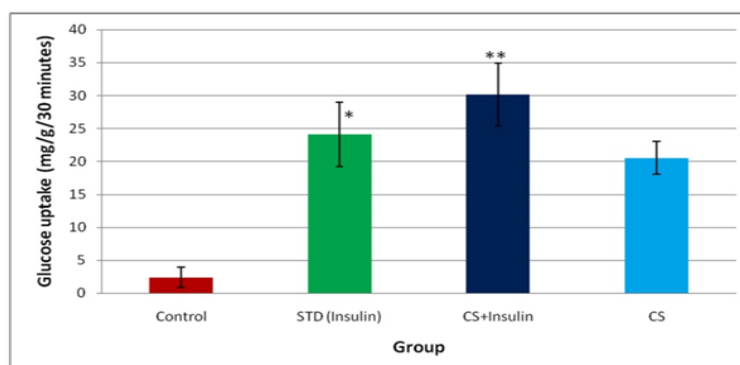


Figure 5: Effect of Insulin and *C. splendens* extracts on *in vitro* glucose utilization capacity by isolated rat diaphragm on normal rats

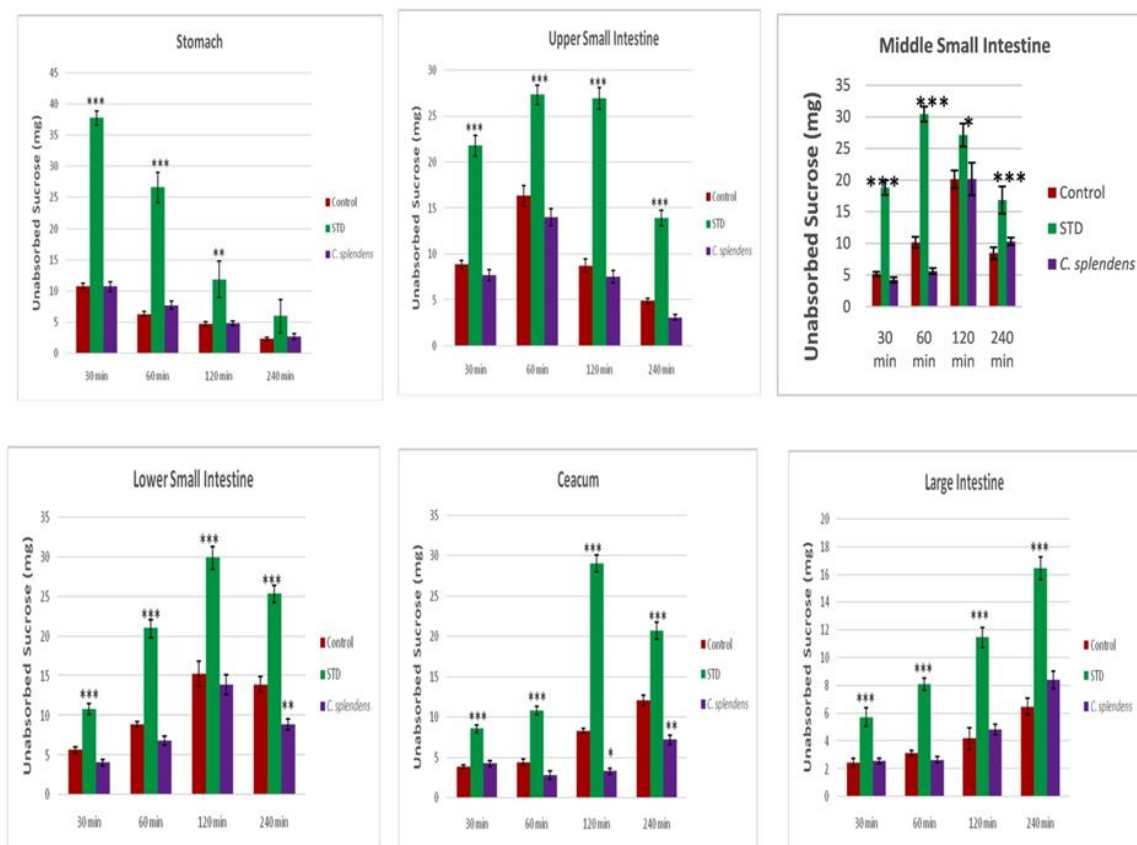


Figure 6: Effect of *C. splendens* on the retention of sucrose in the gut

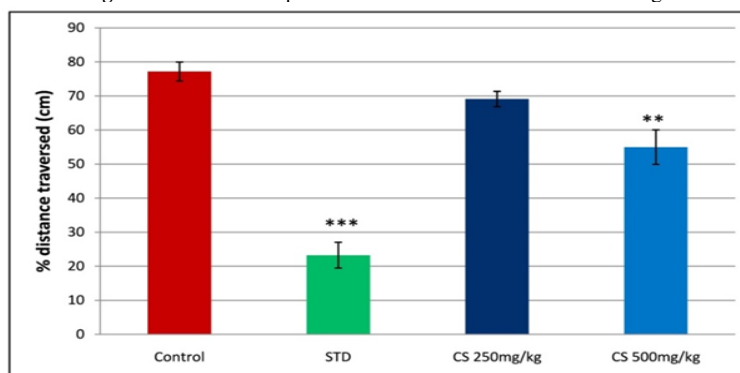


Figure 7: Effect of *C. splendens* on the gastrointestinal motility of barium sulphate milk in mice

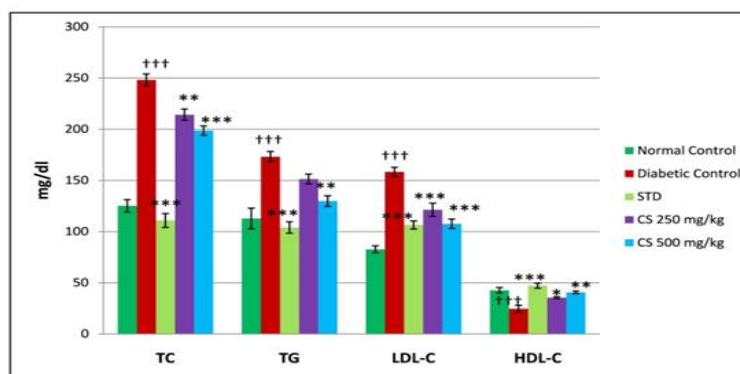


Figure 8: Effect of the ethanolic extract of *C. splendens* (CS) on total cholesterol (TC), triglycerides (TG), LDL-C and HDL-C level after 28 days feeding in type-2 diabetic rats

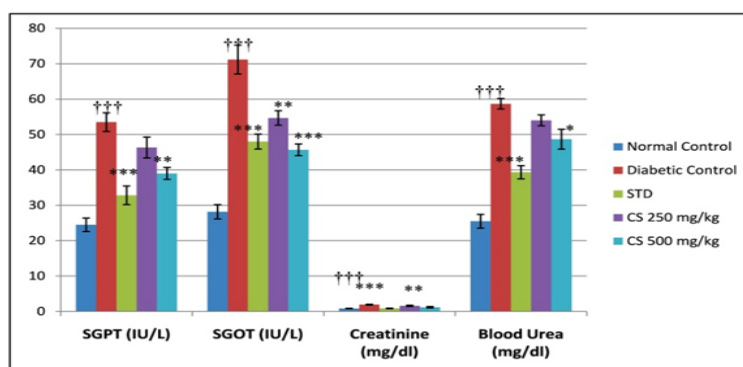


Figure 9: Potential of *C. splendens* (CS) to lower the level of SGPT, SGOT, creatinine & urea after 28 days feeding in type-2 diabetic rats

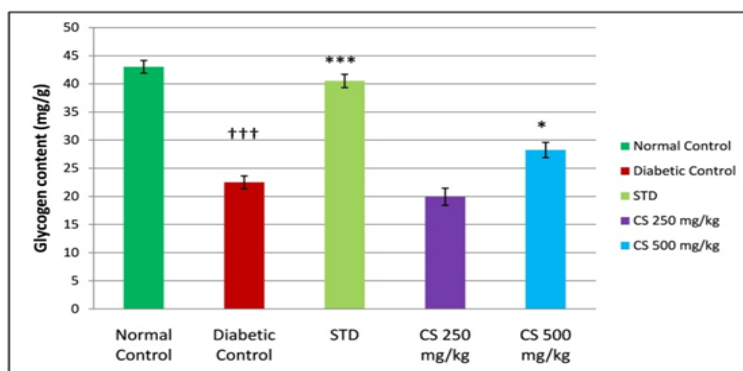


Figure 10: Effect of the ethanolic extract of *C. splendens* (CS) on the liver glycogen level after 28 days feeding in type-2 diabetic rats

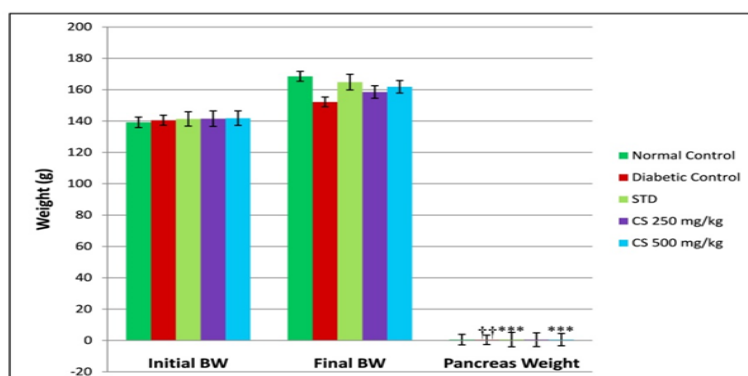


Figure 11: Effect of the ethanolic extract of *C. splendens* (CS) on the body weight after 28 days feeding in streptozotocin induced type-2 diabetic rats

DISCUSSION

In the twenty-first century, diabetes mellitus is one of the most challenging health pandemics. Approximately 347 million people worldwide suffer from diabetes mellitus and by 2030; this figure is predicted to be doubled, making diabetes the 7th greatest cause of death globally [24,25]. Despite significant advancements in the management of diabetes, the synthetic medications currently on the market are linked to mild to severe adverse effects [26]. Instead of treating the underlying pathophysiology of diabetes, oral anti-diabetic medications (OAD) alleviate its symptoms. A new and improved oral anti-diabetic medication from a natural source is therefore required.

The tolerance test of glucose by oral route (OGTT) is a popular approach to assess hypoglycemic activity and detect changes in carbohydrate metabolism after glucose intake. Postprandial hyperglycemia is linked to increased micro and macro-vascular risks in diabetes [27, 28].

The study illustrated that the *C. splendens* extract significantly reduced postprandial hyperglycaemia in diabetic animals in glucose loaded states; which may help manage patients with type 2 diabetes who have postprandial hyperglycemia and insulin resistance [29].

Streptozotocin (STZ) is frequently applied to induce type-2 diabetes in lab animals by selectively destroying insulin-producing β -cells. Its toxicity is primarily due to DNA alkylation, along with oxidative stress, nitric oxide release, ATP depletion, enzyme inhibition, and protein glycosylation. STZ-induced hyperglycemia leads to various complications, making glycemic control essential in diabetes management [30,31]. The 28-day study showed that the CS extract significantly improved glycemic control in diabetic animals likely due to enhanced insulin secretion from remaining pancreatic cells.

Excessive production of glucose in blood reacts with hemoglobin and produces the glycosylated hemoglobin (HbA1c) which is used as the most reliable marker for estimating the level of protein glycation when diabetes mellitus is generated by STZ [32]. Oral therapy of CS significantly decreased the HbA1c level reflecting the decreased protein glycation condensation reactions [33] supporting the hypoglycemic activity of the extract.

This study investigated possible hypoglycemic action mechanisms, such as increased insulin secretion and sensitivity, and inhibition of enzymes that break down carbohydrates, and improved peripheral glucose utilization. Hyperglycemia results from starch hydrolysis by α -amylase and glucose absorption via α -glucosidases [34]. This study

showed that CS extract had a slight, insignificant inhibitory effect on α -amylase, suggesting its antihyperglycemic action may involve mild enzyme inhibition and other mechanisms like enhanced insulin secretion, sensitivity, or glucose utilization.

The rat diaphragm method was used as a reliable *in-vitro* approach to assess peripheral glucose utilization [35]. Insulin transports glucose in the isolated rat diaphragm [36]. From the result, CS in combination with insulin facilitated the glucose utilization by rat diaphragm which was more pronounced than the effect of insulin alone suggesting some extra pancreatic mechanism like glucose uptake by peripheral tissues or skeletal muscles by the CS extract.

Sugars are mainly absorbed in the lower GI tract, but disaccharides like sucrose must be broken down into monosaccharides first [37]. High residual sucrose suggests impaired digestion and absorption, leading to excretion. CS treatment retained sucrose in the lower intestine and caecum, indicating its hypoglycaemic effect may partly result from reduced sucrose digestion and glucose absorption.

The rate of gastric emptying and movement of carbohydrates into the small intestine are key element in maintaining blood glucose homeostasis [38,39]. Reduced transit time lowers digestion and absorption of di- and polysaccharides, leading to a reduced post-meal glucose peak [40]. CS extract inhibited GI motility, suggesting its hypoglycemic effect is due to peripheral glucose utilization or insulin secretion, beyond slight α -amylase inhibition.

This study also estimated the changes in some other biochemical parameters like lipidemic status, liver glycogen, serum creatinine, blood urea, SGPT and SGOT in type-2 model rats.

Lipids play major roles in membrane permeability, fluidity and serve as a precursor of bile acids, steroid hormones, fat-soluble vitamins, in metabolism as energy sources and transporters of fat in diet [41,42]. But alteration in the serum lipids is also likely to increase the risk for coronary heart disease [43]. Another characteristic of long-term type-2 diabetes is a change in lipid metabolism. STZ-induced diabetic rats displayed dyslipidemia with high TC, TG, LDL-C and reduced HDL-C [43,44]. Oral CS extract significantly reversed these changes, indicating strong hypolipidemic effects suggesting potential in managing atherosclerosis and vascular complications in type-2 diabetes.

Glycogen is the storable form of glucose, regulated by insulin through enhanced synthesis and inhibition of breakdown [45]. STZ-induced diabetic rats showed reduced liver glycogen, while CS extract treatment significantly restored its level, suggesting enhanced insulin action or secretion, warranting further investigation of serum insulin levels.

STZ-induced diabetes elevates SGPT and SGOT levels, indicating damage to the liver, due to increased liver cell membrane permeability and enzyme leakage into the bloodstream [46]. The observed reduction in these enzymes following CS extract treatment suggests improved metabolism indicating the extract's hepatoprotective potential. Serum creatinine and blood urea are key indicators of kidney function. In STZ-induced diabetic rats, elevated levels reflect impaired renal filtration and diabetic nephropathy due to glucose overload, oxidative stress, and osmotic diuresis [47,48]. Treatment with CS extract lowered these levels, suggesting its protective role against renal damage in type-2 diabetes.

Hyperglycemia in diabetes leads to body weight loss due to muscle wasting from protein degradation. STZ induces weight loss through DNA alkylation and organ damage. An increase in weight of body and reduced glucose in the blood suggests improved glycemic control [49,50]. Treatment with CS extract partially reversed weight loss, indicating reduced muscle wasting and better glycemic regulation. STZ also damaged the pancreas, and the amelioration of pancreas

health by CS extract suggests its protective and anti-diabetic effects in type-2 diabetic rats.

CONCLUSION

The experimental outcomes confirmed the anti-diabetic activity of *C. splendens* by the slight inhibition of α -amylase enzyme and increased utilization of glucose by diaphragm. It also improves diabetic complications like nephropathy and improves lipidemic status. Further investigations need to estimate insulin level and to fully elucidate the mechanisms of the plant extract. Therefore, this plant is an effective alternative in the treatment of type-2 DM.

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Ethical statement

Approval was taken from the animal ethical committee of the Jahangirnagar University to conduct all animal experiments (Ref No.: BBEC, JU/M 2018 (12)2).

Author Contributions

MJA contributed to the investigation, data collection, data analysis, and preparation of the initial draft of the manuscript. SA and MMR contributed equally to the investigation and data collection. MS contributed to the study design, methodology, overall supervision, and critical revision and finalization of the manuscript. All authors reviewed and approved the final version of the manuscript.

Data Availability Statement

The data that support the findings of this study are available and will be made available upon request.

Use of AI in Drafting of Manuscript

The authors declare that they have not used any generative AI/AI-assisted technologies in the writing of this manuscript.

Conflict of interest

The authors declared no conflict of interest.

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