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Exploring the Antidiabetic and Antioxidant Potential of *Celastrus paniculatus* Roots Extract: Insights from preclinical studies

Research Article

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Abstract

Background: Diabetes mellitus is a metabolic disorder that results from elevated blood glucose and reduced starch intake capabilities. Acute hyperglycemia has implications that entails renal deficiencies, neuropathy and even raised cardio vascular risk with long standing hyperglycemia. Objectives: The purpose of this study was to assess the Antidiabetic and Antioxidant Potential of *Celastrus paniculatus* Roots Extract. Material and Method: Wistar rats were fed with High fat diet for 2 weeks and on the 15th day they were injected intraperitoneal with streptozotocin (35 mg/kg) and the rats were treated with *Celastrus paniculatus* (150mg/kg, 250 mg/kg and 300mg/kg) and metformin (10 mg/kg) until the 28th day. The intraperitoneal glucose tolerance test and insulin tolerance test were performed on the 28th day. Furthermore, dynamic blood sugar and lipid metabolism were assessed by measuring fasting blood glucose, fasting insulin, total cholesterol, and triglyceride concentrations. Results: Both metformin and MECP showed considerable depletion in the plasma glucose levels when used in the treatment of animals with T2DM. In the same context, the present work revealed that *Celastrus paniculatus* has hepatoprotective effect as observed by a significant decrease in the liver markers of oxidative stress and levels of serum liver enzymes (ALT and AST) that help in sustaining of β cells. Based on these results, CEPC has the prospect of exhibiting antioxidant and antidiabetic properties and has the possibility of addressing the issue of diabetes mellitus before its occurrence. Conclusion: Therefore, the result of this study suggests that *Celastrus paniculatus* has Antidiabetic and Antioxidant Potential against T2DM.

Keywords: Diabetes Mellitus, *Celastrus paniculatus,* Hyperglycemia, Streptozotocin, Oxidative damage.

Introduction

Diabetes is depicted as a metabolic disorder indicating resistance towards glucose as well as chronic hyperglycemia that can be defined as an elevated blood glucose level. This condition arises when the body does not produce enough insulin to meet its needs, either due to reduced insulin secretion or action, alone or combination of both(1). Long-term microvascular complications affect kidneys, skin and nerves while they are also risk factor for cardiovascular diseases (CVD) associated with diabetes mellitus characterized by hyperglycemic condition.(2) It occurs when the body does not produce enough insulin to meet its demands, either due to reduced secretion or action of insulin or both. These problems arise from incorrect regulatory systems relating to the transportation and storage of metabolism products for example carbohydrate, lipid, as well as protein's catabolism and anabolism that are influenced by inadequate insulin levels or ineffective use of this hormone alone or together. Chronic hyperglycemia associated with diabetes has been associated with fairly frequent long-term microvascular complications such as skin, kidneys, and nerves plus increased chances of getting cardiovascular disease (CVD) (3). This is a very broad topic due to the various types of the disease which have diverse etiologies and pathophysiological mechanisms. According to WHO 2014 data,7 % among adults above 18 were affected by diabetes Melitus; 1.5 million deaths were attributed to it in 2019 (48% of them occurred before age 70); diabetes also caused 460000 deaths linked to kidney failure; furthermore high blood sugar contributed 20% of deaths caused by CVDs .(4)

Diabetes comes in four primary forms: About 10% of individuals with diabetes have T1DM, which is an autoimmune disorder that arises from insufficient insulin production by the pancreatic beta cells. 90-95% of those with diabetes have type 2 diabetes, a complex endocrine and metabolic disease brought on by a confluence of environmental and hereditary factors. Gestational diabetes mellitus affects around 7% of pregnancies annually & is associated with increased mother and prenatal morbidity. The fourth group consists of distinct forms of diabetes, like neonatal

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diabetes, monogenic diabetes, and idiopathic diabetes (5). Several factors, such as obesity, excess glucocorticoids, excessive growth hormone, gestational diabetes, lipodystrophy, ovarian polycystic disease, and genetic mutations, play a role in causing insulin resistance and diabetes (6).

Type-1 diabetes mellitus

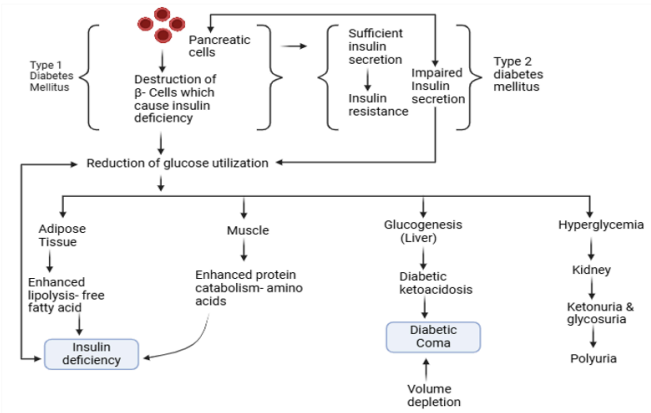
T1DM is an autoimmune condition causing the destruction of insulin-producing cells within the pancreatic islets. This condition is typically brought on by stimulated CD4+ and CD8+ T cells and macrophages that have entered the islets. Juvenile onset diabetes (T1DM) is a type of diabetes that often develops in adolescence and early adulthood (before 35 years of age).(7)

Type 1 diabetes is caused by autoimmune responses in which macrophages and CD4+ and CD8+ T lymphocytes infiltrate the pancreatic islets, resulting in insulitis and the selective death of beta cells. High-risk HLA haplotypes, including DR3-DQ2 and DR4-DQ8, are associated with these responses. HLA class II molecules on antigen-presenting cells (APCs) are essential for activating CD4+ T cells, which then activate CD8+ T cells.(8) Autoimmune vulnerability and beta-cell death are linked to malfunctioning macrophages, which may both secrete pro-inflammatory cytokines and remove cell debris. In addition to causing cell necrosis or apoptosis, local cytokine release can also impair beta-cell function. PGE-2 worsens hyperglycemia by preventing the release of insulin.(9) In pancreatic autopsies of individuals who died shortly after type 1 diabetes onset, the presence of APCs, CD4+, and CD8+ T cells highlights their role in inflammation and beta-cell destruction, with autoreactive CD8+ T lymphocytes playing a major role in the autoimmune death of beta cells.(10)

Type- 2 Diabetes mellitus

T2DM is characterized by insulin resistance and decreased insulin secretion in people, often before the clinical manifestation of the disease. It mainly occurs in those of age 40 and above, though it can start at a younger age in areas of placebo prevalence; it affects at least 90% of the global population. T2DM is known to be typed as non genetic obesity and genetic obesity induced diabetes**.**(11) The pathophysiology involves multiple factors, including changes in pancreatic islet cells, which lower the phases of insulin response, glucose intolerance, and insulin release sensitivity to amino acids**(**12**).** Hyperglucagonemia impairs islet mass and structure through increased beta cell death and decreased neogenesis, with increased alpha cell mass accompanied by islet amyloid polypeptide, or amylin, that plays a role in insulin resistance.(13) IAPP is co localised with amyloid deposits in the islets and plays a role in insulin resistance. Dietary changes such as the intake of high-fat foods, obesity, aging, stressful conditions in life, oxidative stress, and genetic loops such as the PPARG gene also cause T2DM.(14) The sick downward interdependence between pancreatic cells and other influences causes beta cell abnormally, high blood sugar, and the inability of the body to respond effectively to insulin.(15)

Figure 1: Pathophysiology of Diabetes Mellitus



The last several thousand years have seen major developments in diabetes therapy. Type 1 diabetes is still treated exclusively with insulin today. Various classes of medications known as oral hypoglycemic agents were developed such as sulfonylureas including Tolbutamide and Glibenclamide or Glipizide; biguanides including Metformin or Phenformin or Buformin; thiazolidinediones like Rosiglitazone, Pioglitazone or Troglitazone; alpha-glucosidase inhibitors like Miglitol, Acarbose Voglibose; peptide analogs; GLP-1 receptor antagonists and DPP-4 inhibitors etc.(16). *Aloe Vera, Aloe barbadensis, Babul, Neem, garlic, onion, Caesalpinia bonducella, bur, gudmar*, and other medicinal plants have all been used to cure diabetes since ancient times.

Some local herbs traditionally used to manage diabetes include aloe vera, neem, garlic, and onion. (17)*Celastrus paniculatus*, known as the staff tree or black oil plant, also holds medicinal properties and is found in regions like northern India, Indonesia, Laos, Maharashtra, Orissa, and the Andaman Nicobar Islands. (18,19)

Celastrus paniculatus contains a number of secondary metabolites such as protein, amino acids, polyalcohol's, alkaloids, glycoside, tannin, fatty acid, phenolic, flavones, saponin and sterols. These metabolites are said to contribute to the pharmacological activity of the plant and the identified activities are including hypolipidemic, anti-oxidant, anti-depressant, anti-fertility, nootropic and neuroprotective (20,21). These diseases include depression, asthma, cough, sleeplessness, leprosy, leucoderma, epilepsy, gout, fever, paralysis, rheumatism, dyspepsia and cognitive impairments that in one way or the other it was used in the past to treat. *Celastrus paniculatus* has a reasonably proven medical efficiency but the process of how it works and its efficiency in treating diabetes more need to be explored. Therefore, in an effort to draw attention to the possibility of plant's use in diabetes treatment, researchers are trying to establish the yield of *Celastrus paniculatus* root extract in terms of antioxidant and antidiabetic activity in the animals. (22-23)

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Material and method

Extraction of Plant Material

The roots of *Celastrus paniculatus* are extracted using a methanolic extraction method. The roots are shade-dried for two weeks, then ground into a coarse powder. The extraction is carried out by refluxing the mixture for three hours with water and 50% v/v methanol in a 1:10 (w/v) drug-to-solvent ratio using a Soxhlet apparatus. After filtration, the resultant extracts are vacuum evaporated and oven-dried at 40 °C to produce a brown residue, which is stored at 4 °C until needed.(20)

Drugs and Chemicals

- **Test drug:** Roots of Plant *Celastrus paniculatus* were procured from Himachal & were authenticated from CSIR-National Institute of Science Communication and Information Resources (NISCAIR), under Reference No. NISCPR/RHMD/ CONSULT/2023/4338-39.The roots were dried for two weeks before being crushed into a coarse powder and refluxed with a solvent (Methanol) to produce plant extract.
- **Standard drug:** Metformin was mixed with sterile saline and fed orally to rats at a dose of 10 mg/kg**.** (22)
- **Streptozotocin (STZ):** STZ 35 mg/kg was given intraperitoneal after being freshly dissolved in 0.1 mol/L of pH 4.5 citrate buffers.

Induction of Diabetes

For the induction of diabetes mellitus, animals were fed a high-fat diet for two weeks. On the fifteenth day, an intraperitoneal injection of streptozotocin (35 mg/kg) was administered, leading to insulin resistance and partial damage to pancreatic beta cells. After 72 hours of STZ induction, plasma glucose levels were measured by taking blood samples using the retro-orbital plexus technique and a capillary glass tube. (24)

Figure 2: **Experimental Design**

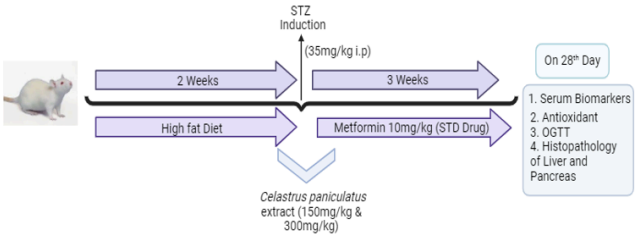


Table 1: Composition of high fat diet (24)

Chemical	Composition
Chow diet	67.5%
Sucrose	20%
Pig lard	10%
Custard powder	2.5%

Animals

Adult male Wistar rats weighing 180–200g were obtained from AIIMS in New Delhi. The animals were held in quarantine until their health condition was monitored and then transported to the housing area. Prior to the studies, the animals were acclimatized for seven days to the living conditions at the ASBASJSM College of Pharmacy, Bela's Central Animal House Facility. The animals were kept in polypropylene cages with bedding made of dust-free rice husk and normal laboratory conditions, which comprised a controlled temperature of 23 2°C, a humidity of 40 10%, and a natural cycle of light and dark lasting 12 hours each. The laboratory mice were cared for in compliance with CCSEA, Ministry of Forests & Environment, and Government of India guidelines. They were fed a normal mouse pellet diet (Ashirwad Industries, Mohali) and given clean water on a continuous basis.

Experimental Protocol

The animals were divided into six groups, each with six animals (n=6)

1. **Group 1- (Normal Control):** Animals were administered with 0.9% normal saline (p.o) and a standard chow diet was provided for all the study period of 28 days.
2. **Group 2- [High fat diet (HFD) + Streptozotocin (STZ)]/Diabetic Control:** Animals were administered with high fat diet for two weeks and STZ was injected on 15th day after two weeks of HFD. Blood glucose level were measured weekly for 21 days after the induction of STZ.
3. **Group 3- [High fat diet (HFD) + Streptozotocin (STZ) + Standard (Metformin)]:** Animals were administered with high fat diet for two weeks and STZ was injected on 15th day after two weeks of HFD. Standard treatment of metformin at the dose of 10mg/kg (p.o) was started on 18th day after 3 days of STZ induction.
4. **Group 4- [High fat diet (HFD) + Streptozotocin (STZ) + Methanolic extract of *Celastrus paniculatus* (MECP^{1})]:** Animals were administered with high fat diet for two weeks and STZ was injected on 15th day after two weeks of HFD. Treatment of test drug *Celastrus paniculatus* extract (MECP^{1}) at the dose of 150mg/kg (p.o) were started on 18th day after 3 days of STZ induction.
5. **Group 5- [High fat diet (HFD) + Streptozotocin (STZ) + Methanolic extract of *Celastrus paniculatus* (MECP^{2})]:** Animals were administered with high fat diet for two weeks and STZ was injected on 15th day after two weeks of HFD. Treatment of test drug *Celastrus paniculatus* extract (MECP^{2}) at the dose of 250mg/kg (p.o) were started on 18th day after 3 days of STZ induction.
6. **Group 6- [High fat diet (HFD) + Streptozotocin (STZ) + Methanolic extract of *Celastrus paniculatus* (MECP^{3})]:** Animals were administered with high fat diet for two weeks and STZ was injected on 15th day after two weeks of HFD. Treatment of test drug *Celastrus paniculatus* extract (MECP^{3}) at the dose of 300mg/kg (p.o) were started on 18th day after 3 days of STZ induction. Blood glucose levels were measured weekly for 21 days after treatment, demonstrating sustained glycemic control throughout

the treatment period. The results indicated a progressive reduction in blood glucose levels, highlighting the effectiveness of the regimen. At the end of study on 28th day all the biochemical parameters were measured and animals were subjected for tissue analysis and histopathological examination.

Assessment of serum biomarkers

At the conclusion of the study, the serum biomarkers were evaluated. Under the right anesthesia, blood was drawn by puncturing the retro-orbital plexus with glass capillary tubes. At the end of the experiment, Blood samples were drawn, and plasma or serum was separated for analysis of various hematological parameters such as blood glucose level, OGTT, AST, ALT), and lipid profile (cholesterol, triglyceride). All analyses were carried out using an auto analyzer and commercially available kits.

Estimation of Blood Glucose Level

The concentration of glucose found in human and other animal blood is generally referred to as the "blood glucose level." The normal blood glucose level is less than 100 mg/dl, & two hours after eating, it is less than 140 mg/dl. However, blood glucose levels that are higher than these normal ranges can easily be detected by a glucose meter and result in the serious complication known as diabetes mellitus. In this study, we'll also use a glucose device to measure the animals' blood glucose levels once a week.

Estimation of OGTT in Postprandial Non Diabetic Rats

The animals were divided into four groups and fasted overnight before the oral glucose tolerance test. Normal control group (Group 1), standard group (Group 2), low dosage MECP1 (Group 3), high dose MECP2 (Group 4), and then all animals were challenged with glucose 2 g/kg orally 30 minutes after the medication treatment was administered. Before, 30, 60, and 120 minutes after the glucose loading, blood samples are taken, and blood glucose levels are then evaluated using a glucometer. (25,26)

Statistical analysis

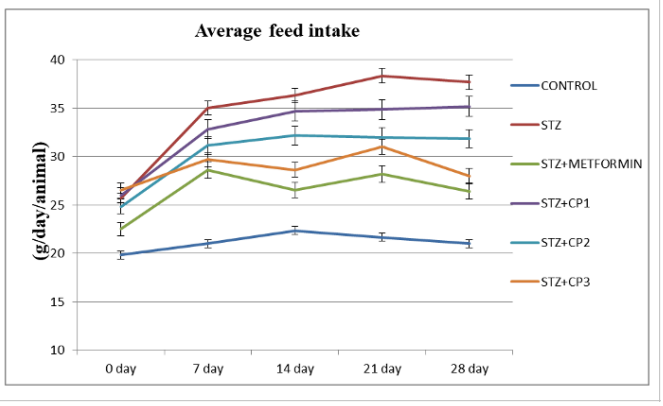
The data were expressed as mean ± standard error of mean (SEM). The data was analyzed using a one-way ANOVA followed by Tukey's multiple comparison tests or a two-way ANOVA followed by Bonferroni's post hoc test using Graph Pad Prism 5.0 software package. A value of $p < 0.05$ was considered to be significant.

Results

Effect of MECP on Feed Intake

STZ group shows significantly increased in feed Consumption on 7th, 14th, 21st & 28th day as compared to normal control group. The feed Consumption of **STZ+Metformin** on 14 th , 21st & 28th, **STZ+MECP2** on 21st & 28th and **STZ+MECP3** on 14th, 21st & 28th reduced as compared to **STZ** group. However, the Peak effects were observed on 28th day. (Figure: 2)

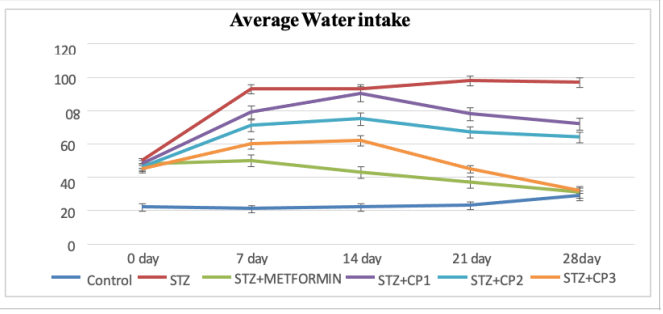
Figure 2 : Effect of MECP on Feed intake



Effect of MECP On Water Intake

STZ group shows significantly increased in water intake on 0, 7th, 14th, 21st & 28 th day as compared to normal control group. The water intake of **STZ+ Metformin** on 7th, 14th, 21st & 28th, **STZ+MECP$_2$** on 21st & 28th and **STZ+MECP$_3$** on 14th, 21st & 28th reduced significantly as compared to **STZ** group. However, the Peak effects were observed on 28th day. (Figure 3)

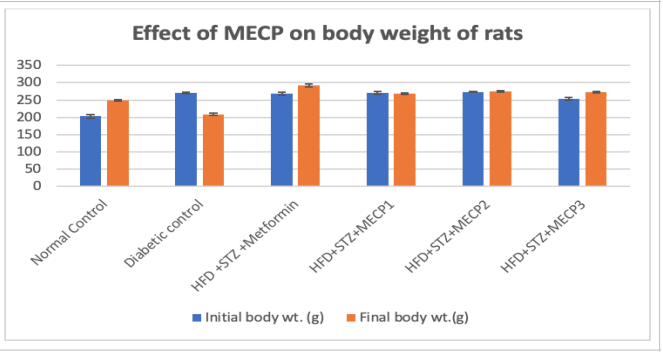
Figure 3: Effect of MECP on Water intake



Effect of MECP on body weight of rats

STZ group shows significantly decreased in body weight on final day as compared to normal control group. The body weight of **STZ+ Metformin** and **STZ+MECP$_3$** on Final day increased significantly as compared to **STZ** group. However, the Peak effects were observed on final day. (**Figure: 4**)

Figure 4: Effect of MECP on body weight of rats



Effect of MECP on the fasting blood glucose level

STZ group shows significantly increased in blood glucose level on 0, 7th, 14 th 21st & 28th day as compared to normal control group. The blood glucose

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of **STZ+ Metformin** on 7th, 14 th, 21st & 28th, **STZ+MECP2** on 14 th, 21st & 28th and STZ+**MECP3** on 7th, 14th, 21st & 28th reduced significantly as compared to **STZ** group. However, the Peak effects were observed on 28th day. (Figure:5)

Figure 5: Effect of MECP on the fasting blood glucose level

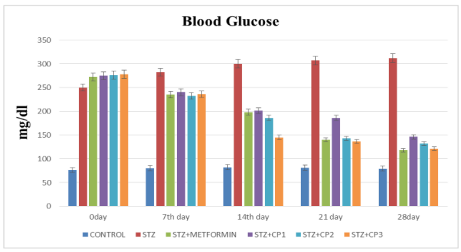


Figure 6: Effect of MECP on OGTT

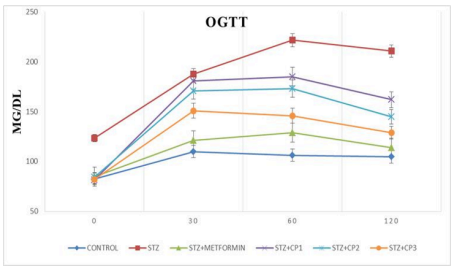
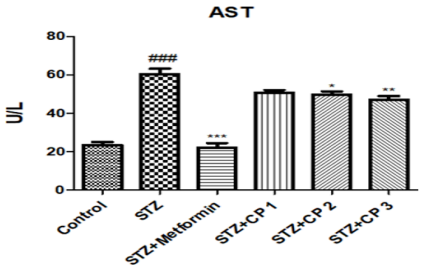


Figure 7 : Effect of MECP on SGOT (AST) level



Effect of MECP on OGTT in postprandial non diabetic rats

STZ group shows significantly increased in blood glucose level on 0 min, 30 min, 60min and 120min as compared to normal control group. The blood glucose of **STZ+Metformin** on 0 min, 30 min, 60 min and 120 min, **STZ+MECP2** on 120 min and **STZ+MECP3** on 60 min and 120 min decreased significantly as compared to **STZ** group. However, the Peak effects were observed on 2th day. (Figure: 6)

Effect of MECP on biochemical parameter and antioxidant enzyme

The efficacy of MECP (150, 250 and 300mg/kg) extract on Hepatic markers was analyzed on the 28th day represent the effect of MECP extract on hepatic markers: serum AST, ALT. These pathophysiological indices in diabetic rats were significantly elevated as compared with normal rats. Oral administration of MECP (150 mg/kg, 250mg/kg and 300 mg/kg) extract to diabetic rats normalized the altered ALT and AST levels in comparison with diabetic rats. But this reduction is not significant. Treatment with MECP (150mg/kg, 250mg/kg and 300 mg/kg) caused reduction of total cholesterol but this is not statistically significant.

Effect of MECP on SGOT (AST) Level

STZ group shows significantly increased AST level as compared to normal control group. The AST level of STZ+ Metformin and STZ+MECP3 (250mg/kg and 300mg/kg) significantly reduced as compared to STZ group. (Figure: 7).

Effect of MECP on SGPT (ALT) level

STZ group shows significantly increased ALT level as compared to normal control group. The ALT level of STZ+ Metformin and STZ+MECP (250 mg/kg and 300mg/kg) significantly reduced as compared to STZ group. (Figure: 8)

Effect of MECP on TBARS Level

STZ group show significantly increased in TBARS levels as compared to the normal control group. The TBARS level of STZ+ Metformin and STZ+MECP 300 mg/kg significantly decreased as compared to STZ group. (Figure: 9)

Effect of MECP on GSH level

STZ group shows significantly decrease in GSH levels as compared to the normal control group. The GSH level of STZ+ Metformin and STZ+MECP (250mg/kg and 300 mg/kg) significantly increased as compared to STZ group. (Figure :10)

Figure 8: Effect of MECP on SGPT (ALT) level

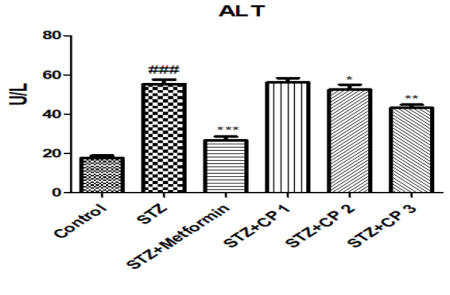


Figure 9: Effect of MECP on TBARS level

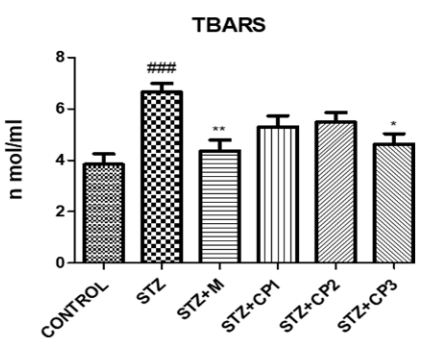
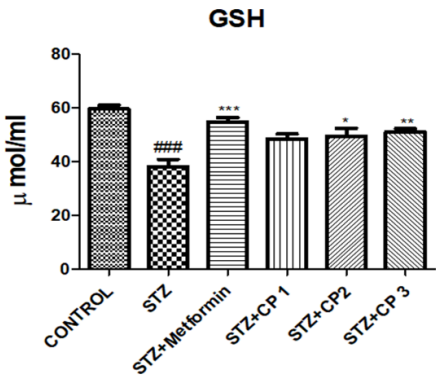


Figure 10: Effect of MECP on GSH level



Effect of MECP on SOD level

STZ group show significantly decrease in SOD levels as compared to the normal control group. The SOD level of STZ+ Metformin and STZ+MECP (250mg/kg and 300mg/kg) significantly increased as compared to STZ group. (Figure: 11)

Figure 11: Effect of MECP on SOD level

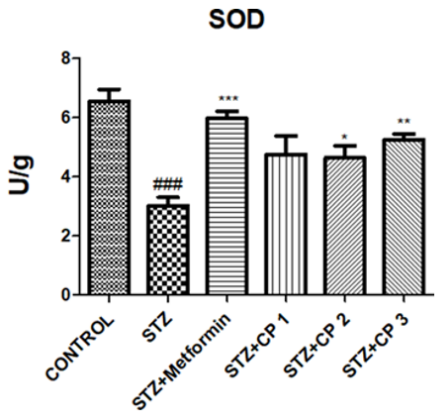


Figure 12: Effect of MECP on Cholesterol level

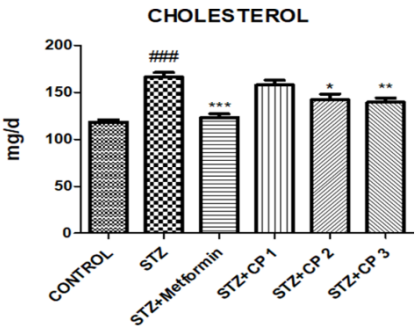
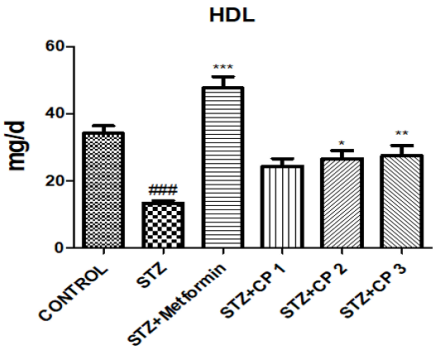


Figure 13: Effect of MECP on HDL Level



Effect of MECP on serum lipid profile

Effect of MECP on Total Cholesterol (TC), High Density Lipoprotein Cholesterol (HDL- C), Low Density Lipoprotein Cholesterol (LDL-C) and Triglyceride (TG). The serum Total Cholesterol (TC), Low Density Lipoprotein Cholesterol (LDL-C) and Triglyceride level were significantly reduced upon administration of MECP (250mg/kg and 300mg/kg) and Metformin treatment.

Effect of MECP on Cholesterol Level.

STZ group shows significantly increased cholesterol level as compared to normal control group. The cholesterol level of STZ+ Metformin and STZ+MECP (250 mg/kg and 300mg/kg) significantly reduced as compared to STZ group. (Figure: 12)

Effect of MECP on HDL Level

STZ group showed significantly decreased in HDL level as compared to the normal control group. The HDL level of STZ+Metformin and STZ+MECP (250mg/kg and 300mg/kg) significantly increased as compared to STZ group. (Figure :13)

Effect of MECP on LDL Level

STZ group show significantly increased the level of LDL as compared to the normal control group. LDL level of STZ+Metformin and STZ+MECP treated (250 mg/kg and 300mg/kg) significantly reduced as compared to STZ group.(Figure :14)

Effect of MECP on Triglyceride Level

STZ group show significantly increased in triglycerides (TG) levels as compared to the normal control group. The TG level of STZ+GL and STZ+MECP (250mg/kg and 300 mg/kg) significantly decreased as compared to STZ group. (Figure: 15)

Histopathological studies

Rat liver tissue photomicrographs of (a) the normal group and (b) the diabetic control group show mild sinusoids, damaged central veins, hepatic cells, and infiltration of inflammatory cells with congestion in the hepatic vein; (b) the normal group shows normal portal triad, normal hepatic sinusoids, hepatic artery, and normal hepatocytes with a hepatic vein; (c) Metformin-treated group, showing tissue regeneration

Figure 14: Effect of MECP on LDL level

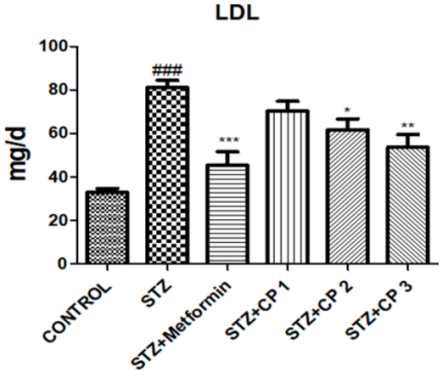


Figure 15: Effect of MECP on Triglyceride level

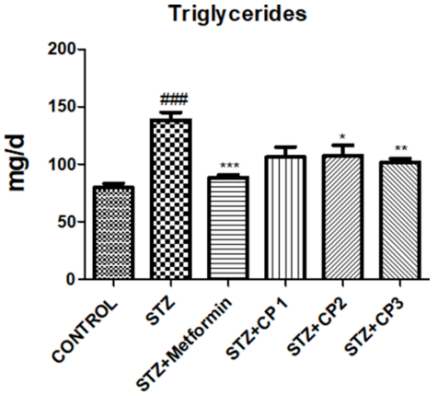
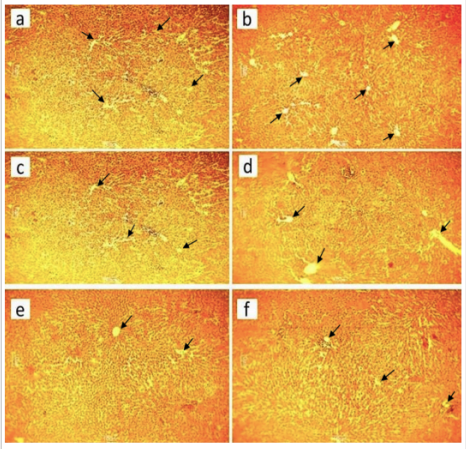


Figure16 : Histopathology of pancreas



and prominent hepatocytes. Normal central vein and sinusoids; (d) and (e) 150 mg/kg and 250mg/kg *Celastrus paniculatus*- treated group, showing mild tissue regeneration change in cellular anatomy; (f) 300 mg/kg *Celastrus paniculatus*-treated group, showing improvement in central vein, regeneration of hepatocytes and improved sinusoids, hepatic artery, hepatic vein, and decreased periportal inflammation.

Rat pancreatic tissue photographed under a microscope, displaying (a) large, spherical clusters of islet cells that are undamaged. (b) The group with diabetes, which had smaller islets of Langerhans and showed degenerative changes in β cells, resulting in a decline in the quantity of functional β-cells; (c) The group treated with metformin, which had more β-cells and acinar cells surrounding the islets, albeit in a normal ratio; (d) and (e) 150 mg/kg and 250 mg/kg group treated with *Celastrus paniculatus* exhibiting no change (e) 300 mg/kg The group treated with *Celastrus paniculatus* exhibited a return to normal pancreatic histology.

Discussion

Diabetes mellitus is now a major concern for global health problem in the twenty-first century and is now one of the non-communicable health disorders with the fastest rate of growth. A chronic multifactorial endocrine metabolic condition called Diabetes mellitus is marked by elevated blood sugar levels.(27) This may be caused by two basic problems: a reduction in insulin levels produced by the pancreatic beta cells and resistance to the effects of insulin at various target tissues (including muscle, the liver, and adipose tissue), which eventually results in a reduced ability to absorb glucose.(28) A "silent epidemic" has been used to characterise diabetes mellitus (DM). It could manifest as a slow, asymptomatic progression that results in loss or coma. It is acknowledged on a global scale as a major source of disease and mortality. By 2030, 7.8% of the world's population, or 366-438 million people, are predicted to develop diabetes, a 54% rise from the estimates made in 2010.(29)

This study aimed to find novel sperable antidiabetic medications for the management of diabetes mellitus (DM). The High-Fat Diet (HFD) and Low-Dosage STZ paradigms were used in the study because these two factors combined create insulin-induced glucose intolerance. Therefore, when treated with the beta-cell toxin STZ, which is comparable to type 2 DM, functional beta-cell mass is decreased.(30) The rat model developed insulin resistance syndrome symptoms after two weeks of high-fat diet (HFD) feeding, including insulin resistance, raised plasma insulin concentration, moderate hyperglycemia, hypercholesterolemia, and obesity. This has been demonstrated to be accurate, since well-researched mechanisms like the Randle (glucose-fatty acid) have been shown to produce what may be called a state of insulin resistance as a result of HFD(31) Increased FA oxidation instead of glucose utilization may lessen the liver's and muscles' sense of insulin, which often results in hyperinsulinemia or insulin resistance. *Celastrus paniculatus* was chosen for a number of reasons, including its metabolites, which include alkaloids, glycosides, flavonoids, saponins, steroids, tannins, and phenolic chemicals. This plant has antioxidant qualities, and its main characteristic is the prevention of reactive oxygen species (ROS) production. Alkaloids, glycosides, tannins, flavonoids, and saponin were discovered by phytochemical analysis of Celastrus paniculatus, whose methanolic extract was utilized in the investigation.(32)

Alkaloids exert antidiabetic effects by inhibiting α-glucosidase and α-amylase, enhancing insulin secretion, and activating AMPK, as seen with berberine (Berberis spp.). Glycosides, like stevioside (Stevia rebaudiana), improve insulin secretion and sensitivity while slowing glucose absorption. Tannins, such as ellagitannins (from pomegranate), inhibit digestive enzymes, reduce oxidative stress, and enhance glucose uptake. Flavonoids, like quercetin (from onions and apples), protect pancreatic β-cells, improve insulin sensitivity, and slow carbohydrate digestion. Saponins, including ginsenosides (Panax ginseng), boost insulin secretion, inhibit digestive enzymes, and modulate gut microbiota. (33-36)

The rat model of type-2 diabetes, generated by HFD and STZ, was used to test Celastrus paniculatus's antidiabetic efficacy. As streptozotocin has a longer half-life (15 minutes), causes persistent hyperglycemia with fewer instances of ketosis, and lowers mortality, it is mostly utilised to study the in vivo antidiabetic effects in rats. When streptozotocin (STZ) enters pancreatic cells through glucose transporter type 2 (GLUT2), it is broken down into glucose and methyl nitrosourea. The methyl nitrosourea has DNA-alkylating properties that damage the beta cells of the islets of Langerhans & eventually triggers the progression to T2DM. This is the crucial foundation of DM.(37,38)

Diabetes brought on by STZ is accompanied by a significant reduction in body weight. Protein waste might be the cause of body weight loss if there aren't any carbohydrates available to use as an energy source. In diabetic rats, oral treatment with a methanolic extract of *Celastrus paniculatus* (300 mg/kg) increased body weight, which might be attributed to better management of blood sugar levels.

The increased level of plasma glucose in STZ induced diabetic rats was significantly lowered by MECP (150 mg/kg, 200mg/kg and 300 mg/kg) administration for 28 days.

The OGTT paradigm was employed to evaluate the changed carbohydrate metabolism following post-glucose administration. At 0, 30, 60, and 120 minutes of administration, a marked increase in glucose tolerance was seen at dosages of the extract of 300 mg/kg. A rise in blood Glycated proteins, such as glycemic control (HbA1C), a measure of glycemic control, is a hallmark feature of diabetes. In diabetic rats, oral treatment of MECP, specifically 300mg/kg, increases the amount of total haemoglobin by suppressing a large rise in glycosylated haemoglobin. There was a drop in AST,

ALT, and total cholesterol levels after treatment with MECP 300mg/kg. A significant rise in the content of plasma TBARS indicates an elevated level of lipid peroxidation that causes tissue damage and a failure of the antioxidant defence mechanism to stop the generation of too many free radicals. MECP and Metformin were given orally to diabetic rats for 21 days; this resulted in a considerable decline in plasma TBARS & an stimulate in GSH and SOD levels.

Conclusion

The Findings of this study indicate that *Celastrus paniculatus* root extract exhibits promising antidiabetic potential in the HFD+STZ-induced diabetes rat model. The extract demonstrated blood glucose-lowering effects, amelioration of biochemical parameters, and histological evidence of pancreatic-cell regeneration. These Observations highlight the potential remedy values of *Celastrus paniculatus* in the management of DM. However, further investigation is needed to validate its efficacy, Safety, and elucidate the underlying mechanisms of action before considering its translation into clinical practice.

Conflict of Interest: No conflict of Interest

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