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SCREENING OF ADIABETIC ACTIVITY OF CRUDE EXTRACT OF *CELASTRUS PANICULATUS* IN ALLOXAN INDUCED DIABETIC RAT MODEL

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Abstract:

Diabetes mellitus is a commonest form of endocrine disorder that is characteristic of hyperglycaemia. This is due to a defective metabolic system of fat, proteins, and carbohydrates leading to major health challenges and lifelong microvascular and macrovascular complications. There is the destruction of beta cells of the pancreas that secrete insulin so that insulin is not produced, or defect in release of insulin, or defects in response to insulin by peripheral tissues, that cause hyperglycemiaThe aqueous extract of seeds of Celastrus paniculatus was chosen for the study of antidiabetic action on Alloxan induced diabetic rats.

The preliminary phytochemical screening showed the presence of alkaloids, flavonoids, tannin, carbohydrates, terpenoids, and fixed oils. The administration of CPSE to experimental rats show hypoglycemic action when one dose of CPSE is administered to normal and fasting rats. Additionally, a good glucose clearing capability is seen in the Oral glucose Tolerance Test.

CPSE further shows a gain in body weight of rats in comparison to diabetic rats that show weight loss. Blood glucose levels over the study time period of twenty one days and HbA1c values are also reduced in CPSE administered groups. Total cholesterol, Triglycerides, and LDL levels are augmented and HDL levels are lessened. This is opposed to the values shown by diabetic rats.

Histopathological studies conjointly indicate protecting results of CPSE on pancreatic cells.

Celastrus paniculatus has shown antidiabetic medicinal action, yet its mechanism is not known. Further study may be encouraged that will add to our knowledge and facilitate diabetes treatment.

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INTRODUCTION:

Diabetes mellitus is a commonest form of endocrine disorder that is characteristic of hyperglycaemia. This is due to a defective metabolic system of fat, proteins, and carbohydrates leading to major health challenges and lifelong microvascular and macrovascular complications. There is the destruction of beta cells of the pancreas that secrete insulin so that insulin is not produced, or defect in release of insulin, or defects in response to insulin by peripheral tissues, that cause hyperglycemia. (1)

There were 246 million cases of diabetes in the world over and 41 million cases in India in the year 2007. This number is estimated to cross 592 million by 2035 world over and 70 million counts by 2005 in India.According to WHO the current count of diabetic patients is 422 million world over. (2)

Plant products have been largely used as drugs and cure for various symptoms. Around 800 medicinal plants have hypoglycaemic action worldwide. Several of which are documented in tradition literature yet many of them are used without thorough information about their phytochemicals and their action on the human body. Since these plant constituents show successful results without side effects and can be conveniently used orally, the WHO has advised assessing these drugs. (3)

The uses of hypoglycaemic drugs have side effects, whereas plant products may be freely available with fewer side effects. Further use of insulin and other oral drugs do not prevent the complication that emerges in the late stage of the disease. The search for drugs of the highest efficiency, no side effect, and actions similar to physiological patterns are sought after. Many researchers have contributed large data about plant action on animals and in-vitro studies. (4)

The ayurvedic treatment using *Celastrus paniculatus* seeds shows an effective change in the human body as it is helpful in curing dysentery, diarrhoea, piles, leprosy, wound healing, rheumatism, gout and Alzheimer's disease. It contains alkaloids, sterols, triterpenoids, flavonoids, saponins and tannins. The present study is carried out to show the antidiabetic property of *Celastrus paniculatus* seeds (5, 6).

MATERIALS AND METHODS:

Preparation of seed extract

The *Celastrus paniculatus* seeds were procured and authentified by Dr. Mohammed Ali Uddin Sheik, Secretary of Unani Research Foundation Hyderabad in Telangana State. The seeds are thoroughly dried and cleaned, and then they are fed into a mechanical grinder in small amounts.

300gm of seed powder was soaked in 600 to 700ml of distilled water for at least 12 hr with stirring at constant intervals. This was heated at 60-70 degrees centigrade to reduce it to half of its volume. The extract was thereafter filtered with the help of muslin cloth. This filtrate was concentrated to get a semi-solid extract that was refrigerated to be used as the need arises.

Phytochemical screening of Seed Extract, CPSE

The *Celastrus paniculatus* seed extract CPSE was treated with various reagents and tests were conducted to study the phytoconstituents by standard methods.

Animals

Male Albino Wistar rats of 150-200gm were used for the experimental study. Rats were bought via a dealer i.e. Sainath Animal Agency in Hyderabad. Institutional Animal Ethical Committee had given approval for procurement and for conducting the study using these animals, approval number IAEC/SUCP/2019/05. The animals were fed with adequate standard pellet diet and water *ad libitum*. They were kept under a standard animal house environment in 12hrs light and dark conditions. Fasted rats were deprived of food for 16 hrs prior administration of the extract.

Hypoglycaemic Study

- This is a single-day study
- It is conducted on normal and fasted rats
- Sixteen rats were taken and divided into four groups
- I st group/Normal receives a dose of distilled water
- II nd group/Standard receives a dose of standard drug, glibenclamide 0.5mg/kg
- III rd group/Test1 receives a lower dose of CPSE i.e,800mg/kg
- IV th group/Test 2 receives a higher dose of CPSE i.e,1600mg/kg
- All the samples are administered via peroral route
- Blood samples are collected to test blood sugar levels in rats at 0, 30, 60 and 120 min.

- Blood sample is collected by tail vein method

Oral Glucose tolerance test

- This is a one day study
- Glucose tolerance study is conducted on normal rats with an adequate supply of food and water ad libitum
- Sixteen rats are taken and divided into four groups, grouping is done as mentioned above.
- All the rats were fed adequately and provided free availability of water and food.
- The rats were administered Distilled water, CPSE doses, and glibenclamide respectively by per oral route.
- All the rats were given 50% glucose solution of 2g/kg body weight by p.o. route, half an hour after CPSE and glibenclamide administration.
- Collection of the blood sample by tail vein method
- Samples are taken 30min after glucose is given and continued at 60min, 90min, and 120 min.

Design for Alloxan induced diabetic study

- Rats are fasted overnight before Alloxan 150mg/kg is administered
- Alloxan monohydrate is dissolved in 0.9%w/v normal saline solution which is stored at a cool temperature
- Single-dose of alloxan is given
- Freshly prepared alloxan is given by i. p. route
- Rats are given 10-20% glucose solution to prevent hypoglycemia that may cause death, 6-8 hrs after alloxan is given.
- 5% glucose solution is given for the next 24hr to prevent hypoglycemia
- Blood glucose is estimated to check diabetes-induced rats on 3rd day. Rats with blood glucose levels more than 250mg/dL are selected for the study.
- Once diabetes is induced, all doses were administered once at a specific time of the day
- The study continues for three weeks after diabetes is induced.
- No fasting of animals is done and rats are given food and water *ad libitum.*

Grouping: 30 numbers of animals were selected for the study and divided into five groups, each group contains six animals.

I. Normal Control – This group of rats are given only distilled water and are not diabetes-induced.

II. Disease/ Diabetes Control –These rats become diabetic after Alloxan (150mg/kg b.w., i.p. route) administration. Thereafter only the vehicle is given.

III. Standard /Reference group – These rats are Alloxan induced diabetic and then treated with antidiabetic standard drug, Glibenclamide 10mg/kg b.w., p.o.in + 0.5 % w/v CMC

IV. Test 1 – In this set rats are administered with 400mg/kg p.o. of CPSE. This is done after the rats are diabetic induced with administration of Alloxan 150mg/kg b.w.

V. Test 2 – This set has rats administered with 800mg/kg p.o. of CPSE, after induction of diabetes with alloxan.

Estimation of body weight:

Weight of rats is taken at the beginning of the study (i.e.0th day) and later every week during the study (i.e.7th, 14th, 21st, 28th days).

Collection of blood samples:

Blood samples are collected by the tailvein method for estimation of blood glucose levels once before alloxan is given and later to confirm the induction of diabetes. Once the study starts blood samples are collected on a weekly basis.

On the last day of study, i.e.28th day blood samples are collected by retro-orbital method for estimation of HbA1c and lipid profile.

Histopathological Study

On the 28th day the rats are sacrificed for removal of pancreas for histopathological evaluation. Pancreas was kept in 10% Formalin solution before histological study.

Statistical Analysis

Statistical analysis was carried out using Graph Pad Prism 8.4.0. All results were expressed as Mean ± SEM. Groups of data were compared with analysis of variance (ANOVA) followed by Dunnett's multiple comparison test to identify significance (i.e. $p<0.001$, $p<0.01$, $p<0.05$) between groups.

RESULTS:

Investigation of Phytochemical Constituents

The qualitative tests performed to detect phytochemical constituents of aqueous extract of *Celastrus paniculatus* seeds showed the presence of alkaloids, carbohydrates, flavonoids, tannins, fixed oils, and proteins.

Percentage Yield

The percentage yield of aqueous extract of Celastrus paniculatus seed extract was observed as 13.7%

Body Weight

The body weight of the disease control group decreased (131.7gm), whereas those of CPSE 400mg (177.2gm) and CPSE 800mg (184.5gm) show an increase. The results of test drug are comparable to standard as Glibenclamide (192.0gm) also showed an increase in body weight.

Shown in Fig 1.

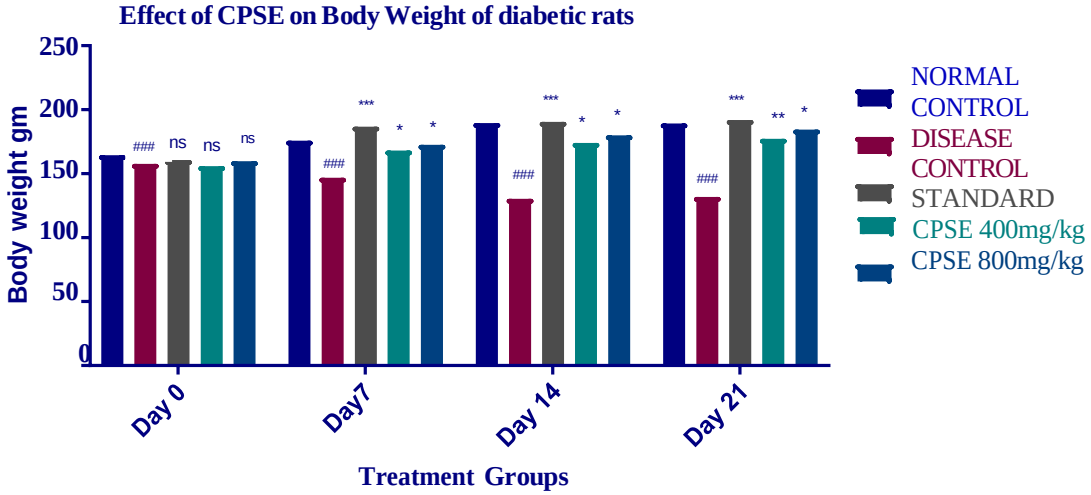

Fig 1.

Hypoglycemic Study of a single dose of CPSE in normal rats.

When a single dose is administered in the groups Glibenclamide shows an evident fall in blood glucose levels at 30 min (54.75 mg/dL). The CPSE 1600mg/kg also shows low blood glucose levels that are comparable to the standard (60.0 mg/dL). Shown in Fig 2.

Oral Glucose tolerance test

The control group shows a maximum glucose level at 60 min, (165.5mg/dL). Glibenclamide administered group show a value of 111.0 mg/dL. The CPSE 400mg and CPSE 800mg also show values 121.8mg/dL and 108.5mg/dL, suggesting hypoglycaemic action. Shown in Fig3.

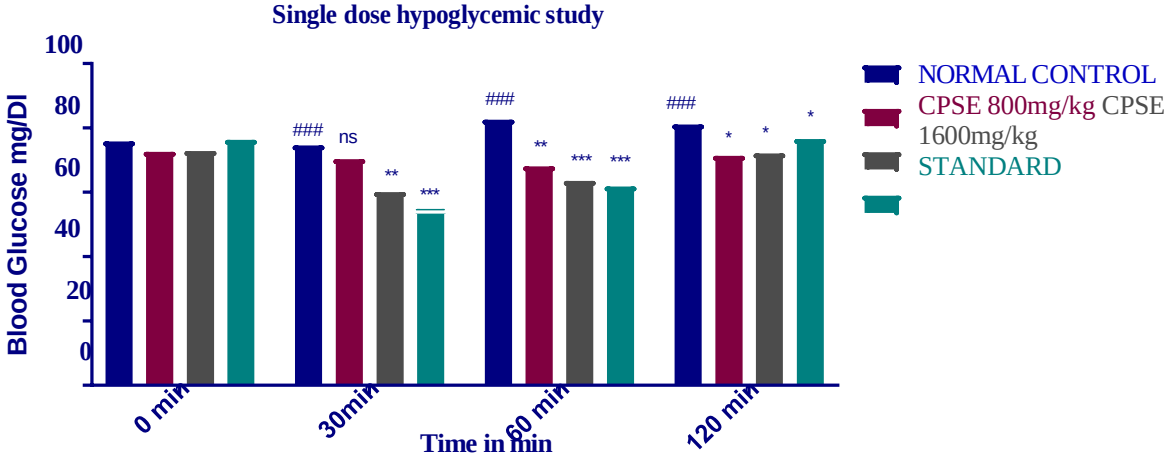

Fig 2.

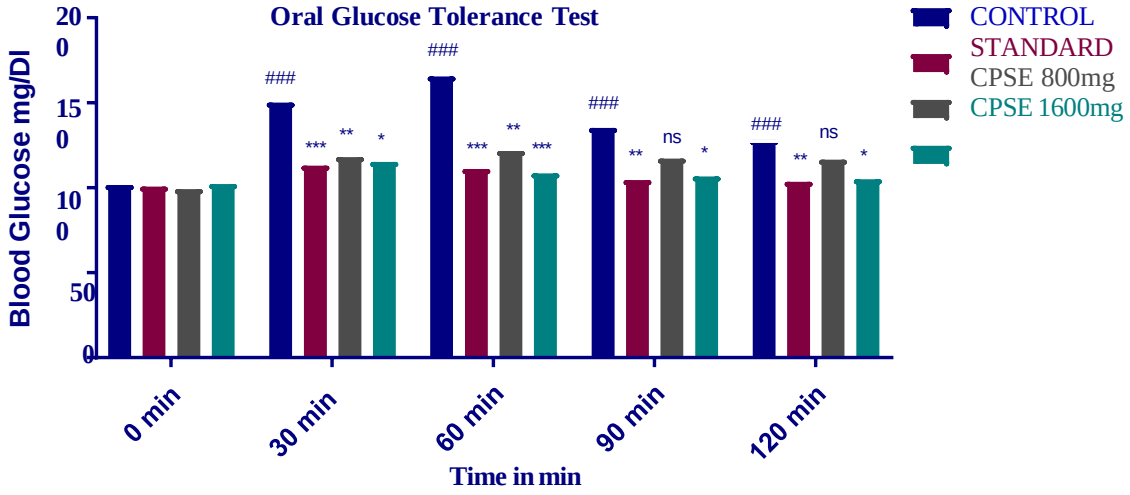

Fig 3.

Blood Glucose

The disease control group showed blood glucose level of 311.7 mg/dL and Glibenclamide 5mg/kg treated group showed a decreased blood glucose level of 128.5 mg/dL. There is a decrease in glucose levels of CPSE 400mg/kg and CPSE 800 mg/kg treated groups showed 180mg/dL and 154 mg/dL. The normal control group showed no significant change in blood glucose levels. Shown in Fig4.

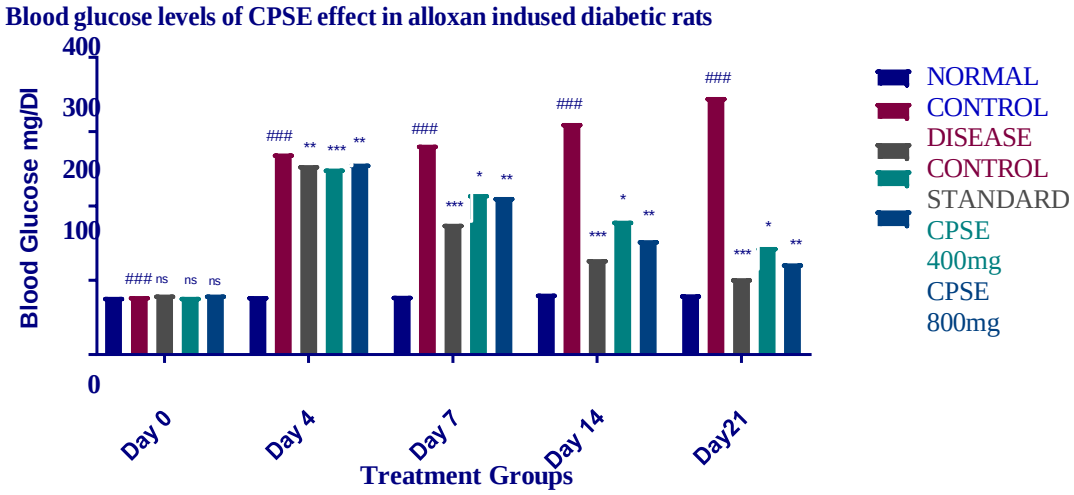

Fig 4.

Histopathology Studies

The sample of the pancreas of rats from the normal control group showed normal size and shape of pancreatic islet cells (A). The samples from the disease control group show a high degree of hypertrophy and hyperplasia of pancreatic cells (B). Glibenclamide treated showed a slight degree of hypertrophy of beta cells(C). Rats treated with CPSE 400mg/kg (D), show pancreas with considerable hyperplasia of beta cells. Samples from CPSE 800mg/kg (E) showed no apoptosis or necrosis and normal acinar cells.

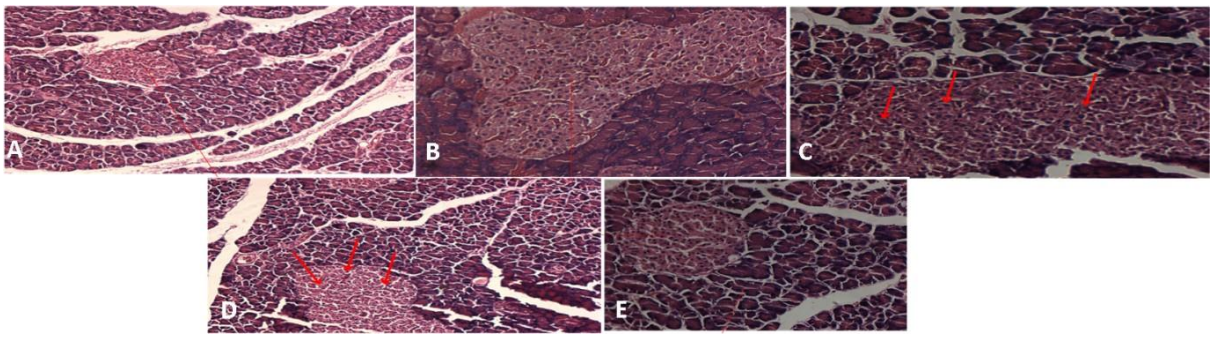

Fig 5.

DISCUSSION:

As diabetes is increasing with a faster pace it has become a major public health concerns worldwide. Controlling not only diabetes but also its lifelong microvascular and macrovascular complications is a challenge. Use of herbal medicines is one of the approaches to treat diabetes and its complications. The conventional treatments may give dissatisfactory effect and herbal treatment may show better glycemic control, availability and affordability. (7).

In this study *Celastrus paniculatus* seeds extract, CPSE is taken to show its hypoglycaemic effect. It is used in hypoglycemic study of a single dose of CPSE in normal rats, shows oral glucose tolerance test (OGTT) and used to treat Alloxan induced diabetic rats. The preliminary phytochemical screening shows the presence of alkaloids, carbohydrates, flavonoids, tannins, fixed oils, and proteins.

A single-dose administration of CPSE 800mg/kg and 1600mg/kg in normal rats show a significant fall in blood glucose levels that are directly proportional to the dose of extract. A maximum reduction in blood glucose levels was observed in one hour for 800mg/kg and 30min for 1600mg/kg and for Glibenclamide (0.5mg/kg). CPSE 800mg/kg showed 68± 3.34mg/dL in one hour and CPSE 1600mg/Kg showed 60±2.08mg/dL while that of Glibenclamide is 54.75±2.28mg/dL in 30min.These results were in accordance with the study conducted by Shah, N.A. and Khan, M.R.(8)

Oral glucose tolerance test (OGTT) consists of prior glucose loading with 50% glucose (2gm/ kg) to experimental rats. The control group showed a rise in blood glucose level of 165.5±4.6mg/dL in one hour. Glibenclamide values are 111 ±3.49 mg/dL, CPSE 1600mg/Kg showing 121.8±1.49mg/dL and CPSE 800mg/kg showing 108.5±4.49mg/dL at one hour. The glucose clearing action of the extract is as good as that of research done by Shalini Adiga et al. (9)

Alloxan induced diabetic rats have shown a significant reduction in the weight of rats. The treatment of these animals with Glibenclamide causes restoration of weight loss. CPSE extract also shows prominent control of weight loss that is comparable with the values of the standard group. The bodyweight of Alloxan induced disease control group on 21st day is 131.7±2.26gm. on treatment with Glibenclamide, the values are reduced to 192±2.74gm. The bodyweight of the CPSE 400mg/Kg administered group is 177.2±1.49gm and that of the CPSE 800mg/Kg treated group is 184.5±1.58gm. These values are in line with the study conducted by Nora A. AlFaris et al. (10)

Glycated hemoglobin is a diagnostic test to check the blood glucose levels over a period of a few months. Alloxan induced disease group show 6.98±0.04% treatment with CPSE 400mg/ Kg and 800mg/Kg show 6.32±0.09% and 6.1±0.13% values resp, the standard group showed 5.760.11%. These results are in accordance with G. Rajiv Gandhi et. al (11)

Diabetes induction with Alloxan 150mg/kg in cold 0.9% normal saline, caused hyperglycemia in the disease control group. Oral administration of Glibenclamide 5mg/Kg and CPSE doses during the study period of 21 days lowered the values of blood glucose level. The Alloxan induced diabetic control group showed 346.7±3.89mg/dL on 21st day of study. The CPSE treated groups of 400mg/Kg and 800mg/Kg also show a marked reduction in blood glucose values of 144.8±2.89mg/dL and

123.7±1.77mg/dL on 21st day of study. The results are closed to the glucose levels of the standard drug that has a value of 102.8±2.65mg/ dL. Such outcomes are in line with the study conducted by R Ghosh. (12)

In the 21 day study, the normal group showed no change in blood glucose level whereas the CPSE and Glibenclamide groups exhibit a notable decrease in blood glucose values; this asserts the antidiabetic action of CPSE. More distinct antidiabetic action was seen by the higher dose of CPSE i.e. 800mg/Kg.

One of the implications followed by diabetes is increased total cholesterol levels and triglycerides. This may be contributed to the fact that insulin deficiency, a reason behind metabolic disturbances, causes a build up of lipids and augmentation of cholesterol and triglycerides.

In the experimental study of the effect of CPSE on total cholesterol levels on 21 days, on Alloxan induced diabetic rats, the total cholesterol levels of the disease control group 154±2.3mg/dL. Glibenclamide treated group showed low values of total cholesterol i.e. 106.33±0.95mg/dL. CPSE treated rats with 400mg/Kg and 800mg/Kg also show such values on lower side i.e. 143.2±1.13mg/dL and 125.8±1.44mg/dL respectively.

Similarly triglycerides and LDL values of the disease control group increase whereas that of the standard group decrease. The action of CPSE on triglycerides and LDL has similar actions to standard and show satisfactory results. On the other hand values of HDL of disease group decrease and standard drug show high levels. The result of CPSE treated rats is complementary to the values of the standard drug. This is in accordance with the study of Shaik Abdul Nabi (13). Hence CPSE also shows antihyperlipidemic action.

The histopathological studies show necrosis of beta cells in the disease control group and on treatment with CPSE 400mg/Kg and 800mg/Kg show moderate hypertrophy and normal beta cell with no apoptosis.

These results indicate the antidiabetic property of *Celastrus paniculatus* seeds.

CONCLUSION:

The aqueous extract of seeds of Celastrus paniculatus was chosen for the study of antidiabetic action on Alloxan induced diabetic rats.

The preliminary phytochemical screening showed the presence of alkaloids, flavonoids, tannin, carbohydrates, terpenoids, and fixed oils. The administration of CPSE to experimental rats show hypoglycemic action when one dose of CPSE is administered to normal and fasting rats. Additionally, a good glucose clearing capability is seen in the Oral glucose Tolerance Test.

CPSE further shows a gain in body weight of rats in comparison to diabetic rats that show weight loss. Blood glucose levels over the study time period of twenty one days and HbA1c values are also reduced in CPSE administered groups. Total cholesterol, Triglycerides, and LDL levels are augmented and HDL levels are lessened. This is opposed to the values shown by diabetic rats. Histopathological studies conjointly indicate protecting results of CPSE on pancreatic cells.

Celastrus paniculatus has shown antidiabetic medicinal action, yet its mechanism is not known. Further study may be encouraged that will add to our knowledge and facilitate diabetes treatment.

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