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AN EMERGENT PLANT '*LEUCAS INDICA*' PLAYS A POTENTIAL ROLE IN TREATMENT OF TYPE II DIABETES

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ABSTRACT

The current study deals with anti-diabetic and pancreatic protective effects of Leucas indica variety Nagalapuramiana extracts in high fat diet (HFD) and streptozotocin (STZ) induced type 2 diabetes model. Ethylacetate extracts were orally administered at the dose of 10, 30 and 100 mg/kg and metformin was used as standard anti-diabetic drug at 10 mg/kg dose orally. Blood glucose, lipid profiles, pancreatic parameters and oral glucose tolerance test (OGTT) were performed. Treatment with extracts resulted significant dose dependent and time dependent decrease diabetes incidence with marked reduction in the blood glucose levels. Glucose tolerance was greatly improved after treatment with plant extracts with high dose group producing effects similar to standard drug mediated beneficial effects. Histopathological studies also indicated pancreatic beta cell protective effects of Leucas indica variety Nagalapuramiana extracts with increased beta cell number and size. Our results demonstrate that Leucas indica variety Nagalapuramiana can be possible remedy to treat type 2 diabetes and associated complications.

KEY WORDS

Diabetes, Leucas indica,Nagalapuramiana, High fat diet, beta cells

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INTRODUCTION

Genus *Leucas* was first portrayed by Robert Brown containing more than 200 species [1]. The variety *Leucas* is one among the 250 genera of the family Lamiaceae which is circulated all through the tropical districts of the earth. It has a place with family Lamiaceae and is normally known as Guma, Tumba, Dandokalos. It is appropriated in South Asia among Bangladesh, India, and Myanmar. It is circulated all over India alongside street side wasteland, waterway banks and rough slopes [2, 3]. It is an erect herb with pubescent fanning, branches slim, puberulous. Leaves are straight laceolate, whole, marginally undulate or serrulate, puberulous on the two sides. Blossoms are white, in whorls at the parts of the bargains elongated, trigonous, earthy black [4]. Customarily, it is utilized in Garhwal district of Uttarakhand as an injury healer.

The leaves of this plant are pressed and set on wounds to acquire wound recuperating [5]. Leaves are additionally utilized as vermifuge, stomachic, narcotic and in bruises. This plant is broadly utilized in psoriasis, ceaseless skin emissions and agonizing [6]. The herb is likewise utilized in jaundice, irritation, asthma, dyspepsia, fever and cold, snake chomps and scorpion stings [7, 8]. The blossoms are given with honey to treat cold and cough in kids. The leaves are applied to the chomps of snakes, toxic creepy crawlies and scorpion sting. L. indica leaves are likewise utilized as bug sprays and mosquito repellent in provincial area. The plant separate with honey is a decent solution for stomach agony and acid reflux

The phytochemicals like phenylethanoid, glycosides were detached from the elevated pieces of *Leucas indica* having cancer prevention agent property [2, 9]. Phytochemical investigation so as to see the nearness of steroids, alkaloids, tannins, proteins, glycosides, sugars, phenols, flavonoids, unstable oils, saponins and starch [10]. Diabetes mellitus is mainly classified by two categories: insulin dependent diabetes mellitus or IDDM (type 1), and noninsulin dependent diabetes mellitus or NIDDM (Type II). Type 1 and type 2 diabetes mellitus (T1D, T2D) have high blood glucose levels (hyperglycemia) in common which can cause serious complications of the vasculature in the advanced stages of the disease [11].

Clinical signs in both types are verified by few frequent symptoms such as excessive thirst, frequent urination, extreme hunger, blurred vision, and severe weakness are the primary symptoms to diagnose diabetes mellitus [12].

MATERIALS AND METHODS

This study was executed at the Department of Pharmacology, University College of Pharmaceutical Sciences, Kakatiya University, and Warangal, India. Collecting the whole plant of *Leucas indica variety Nagalapuramiana,* were validated and checked by a taxonomist. Total cholesterol and triglyceride biochemical test packs were obtained from Accurex (Mumbai, India). Streptozotocin (STZ), hematoxylin and eosin stains were procured from Sigma (Bangalore, India). The various synthetic compounds used in this examination were of research grade quality procured from neighbourhood providers.

Preparation of *the Leucas indica variety Nagalapuramiana*

The whole plant of *Leucas indica variety Nagalapuramiana* were collected and dried at room temperature, until thoroughly dry. The dried plant was ground into a fine powder and sieved through a 40mm work strainer. The acquired powder was kept in water/air evidence plastic sacks. 100 gm of each powdered leaves test was separated with 400ml of methanol with occasional shaking for 7 days by maceration. The move was shifted into a clean conical flask and sieved through a whatman's channel paper into another funnel shaped jar. The methanolic extract of the whole plant was blended with 1000 ml of water freely and fractioned with toluene, ethyl acetate and n-butanol. The solvents were emptied from the parts under decreased strain to yield the relating extract. The ethyl acetate parts of leaves were sifted, dried in a rota-evaporator, and used for further examinations.

Animals: Animal's investigations were executed according to the CPCSEA guidelines of the organization of India. Animal's conventions were affirmed by the Institutional Animal Ethics Committee of the University College of Pharmaceutical Sciences (IAEC/10/UCPSC/KU/2016). Male Sprague Dawley (SD) rats were used for the high fat diet (HFD) notwithstanding STZ (HFD+STZ) induced type II diabetes model and for assessment of protective effect of *Leucas indica*. Animals were acclimatized to the exploratory conditions multi week before the test. Animals were kept up at standard conditions, 12 h day/light cycle, 50-60% relative moistness, nourishment and water provided not indispensable.

Experimental design: Rats were separated into 6 groups with each group containing 10 rats. Out of 10 rats, 6 rats were used for plasma, tissue biochemical and histological examinations and 4 rats were used for oral glucose resistance test (OGTT). The particular rat groups are according to the accompanying: Group1: Normal control-rats feed with standard rat chow diet, Group2: HFD+STZ rats were nourished for about fourteen days with HFD and STZ single organization (35 mg/kg, i.p.) on fifteenth day that is 2 weeks post HFD feeding, Group3: Low dose of extract treated groups, HFD+STZ was given correspondingly and separate treatment was given 1 day post STZ administration onwards till end of assemble at the portion of 10 mg/kg/day, orally, Group 4: Mid dose of extract treated groups: HFD+STZ was given relatively and extract treatment was given 1 day post STZ organization onwards till end of the assessment at the portion of 30 mg/kg/day, orally, Group5: High dose of extract treated groups: HFD+STZ was given similarly and extract treatment was given 1 day post STZ administration onwards till end of the examination at the portion of 100 mg/kg/day, orally and Group6: Standard metformin treated gathering HFD+STZ was given and metformin treatment was given 1 day post STZ administration onwards till end of the assessment at the dose of 10mg/kg/day, orally.

Treatment methodology: For the diabetogenesis and pancreatic beta cell security, rats were treated with selected extract at the dose of 10, 30 and 100 mg/kg orally. Regardless of the preliminary rats from normal control rats were nourished with HFD for around

fourteen days. Following 2 weeks post HFD supporting, rats were induced with STZ to impel diabetes and after that extracts and standard treatment was started on one day post STZ organization. A month of time for testing we have considered in the present work is post STZ treated period. The extracts were suspended in 0.5% Carboxy methylcellulose (CMC) and given orally for 28 days (a month) and first treatment was started on one day after STZ administration. The volume of extracts controlled was kept as 10 ml/kg body weight. Basically, the standard medication of diabetic drug metformin was given orally at the portion of 10 mg/kg.

Induction of type II Diabetes: For induction of type II diabetes, male SD rats were from the start nourished with high fat eating regimen routine for around fourteen days (pre investigative period), trailed by low portion of streptozotocin (STZ) 35 mg/kg was mixed intra-peritoneal (i.p) on around fourteen days present HFD as per well-established method (10). HFD quantity was fixed as 58% fat, 25% protein and 17% starch. In the wake of beginning the metabolic issue like condition due to HFD, rats were injected with single administration of STZ at the portion of 35 mg/kg, i.p. Required proportion of STZ was taken in individual eppendorf tubes and dissolved in overly chilly Citrate buffer pH 4.5. Citrate buffer was added to each individual syringe just before administration to rats. 48 h after the STZ induction, blood glucose levels were evaluated by glucometer. The non-fasting blood glucose levels more than 250 mg/dl were considered as Diabetic rats. The incidence of diabetes was furthermore attested by polyphagic and polydipsic lead of the rats.

Assessment of diabetogenesis in rats: The event of diabetes was assessing by the plasma glucose levels every week. The blood glucose levels were assessed by means of glucometer by collecting the drop of blood from rat's tail. Rats with blood glucose levels >250 mg/dl were considered as diabetic and level of diabetic rats was determined.

Estimation of pancreatic weight: Subsequent to completing of about a month of post STZ time for testing (beginning 2 weeks on HFD is considered pretrial), on day 28 (after a month), blood glucose levels were estimated. Blood was collected to separate plasma and confined plasma was utilized for biochemical assessment of triglycerides and complete cholesterol levels. Rats were euthanized by high dose of anesthesia and pancreas from each rat was detached warily and wet weights of the pancreas were recorded.

Oral Glucose tolerance test (OGTT): Subsequent to completing of about a month of investigative period, a subset of rats from all the experimental groups was utilized to perform oral glucose tolerance test (OGTT). Rats were fasted and administered with 2g/kg portion of glucose orally, following glucose challenge; blood glucose levels were performed by using glucometer at 0, 15, 30, 90 and 120 h post glucose administration. The time versus blood glucose levels were plotted to evaluate the glucose transfer direct of rats and effect of treatment on glucose intolerance.

Histopathological assessment of pancreas: After sacrificing the rats, some piece of the pancreatic tissue was detached and fixed in 10 % formalin. Formalin fixed tissues were set up by the standard histological tissue processing [13]. These processing steps includes dehydration of tissues by presenting to dynamic increasing concentration of alcohol, the last advance of drying out is done with 100% (absolute alcohol). Consequent to fixing the tissues for xylene clearing step, paraffin wax step was performed, and paraffin embedded squares were prepared. These squares were cut into 5 µm thick sections with microtome (Leica, Germany) and stained with hematoxylin and eosin (H&E). Stained sample were seen under light microscopes lens for histological changes. The quantity of pancreatic beta cells and their sizes were evaluated from each slide and estimation was finished.

Statistical Analysis: All the investigative values were communicated as mean ± standard error of mean (SEM). The statistical significance among the groups was investigated by one-way examination of change (ANOVA) trailed by Tukey's multiple comparison test. P value <0.05 is considered as statistically significance.

RESULTS

Effect of *Leucas indica variety Nagalapuramiana* extract treatment on blood glucose levels: The blood glucose levels were estimated during a month of preliminaries in all the experimental groups, at the basal levels (2 weeks post HFD sustaining), there it was a 1.35 fold increase in the blood glucose levels in all the HFD experimental animals, is average, in perspective on high vitality substance accomplished mellow hyperglycemia. Upon STZ organization, noteworthy increase in the blood glucose levels was seen in HFD+STZ control when compared with control rats. The

glucose levels supposedly were continuing 3.65-fold increasing till the test length of about a month (28 days). The hyperglycemic condition found in diabetic control animals was portion conditionally brought down in concentrate treated groups. The ethyl acetate fraction of leaves extract at 100 mg/kg passed on exceedingly significant decrease 2.30-fold in the blood glucose levels before 28 days of treatment. The high dose fraction indicated hypoglycemic effect like standard drug metformin 2.85-fold. Low 1.21 folds and mid 1.66-fold portion of extract treatment came about smooth to direct control in blood glucose levels. Figure 1 clarifies the blood glucose profile of various groups for 28 days post STZ organization and impact of focus and standard medication on glucose profiles.

Effect of *Leucas indica variety Nagalapuramiana* extracts treatment on Diabetogenesis and diabetes incidence: Figure 2 noticeably displays that at the basal levels (2 weeks post HFD encouraging) none of the experimental rats were seen to be diabetic. The normal blood glucose levels were seen to be lower than the diabetic levels (250 mg/dl). 7 days post STZ induction; we can unmistakably watch the best increment in the degree of diabetes over 50% rats in untreated HFD+STZ rats. The degree of diabetes was seen to be 83.3% in fourteen days and 100% by around 21 days post STZ treatment and same level was kept up to 28 days. Curiously, treatment with extracts at all three doses levels has shown decline in the degree of diabetes with best diminishing in the diabetes rate in high dose treated rats 67% reduction, mid dose treated rats 50% , low dose treated rats 16% in the diabetes possibility. When we observed at the last time point (28 days) recurrence of diabetes, unmistakably demonstrated fractions significantly diminished in occurrence of diabetes (Figure 3). The high dose extracts treated rats has displayed the immense decrease in the recurrence of diabetes which is near in degree appeared differently in relation to standard metformin 84%.

Effect of *Leucas indica variety Nagalapuramiana* extract on OGTT: Since OGTT is performed to estimate the status of glucose tolerance and glucose disposal behavior of rats. It is seen from the blood glucose profile that upon glucose challenge the levels were essentially expanded in HFD+STZ rats diverged from control rats. The glucose levels were close to 601.2 mg/dl within 15 min post glucose challenge. Furthermore, these glucose levels have not brought down to conventional levels following 90 min, surprisingly, the glucose levels have diminished in treated rats, (Low dose 301.47 mg/dl, mid dose 266.41 mg/dl, High dose 209.46 mg/dl) which shows close to that of glucose levels in HFD+STZ rats diverged from common control rats. Inquisitively, separate prescriptions have realized huge ramifications for glucose profiles with portion dependant improve in glucose transfer direct. High dose of extracts has institutionalized the glucose bigotry close to ordinary control rats 110.42 mg/dl. Similar kind of improved glucose bigotry was found in metformin treated groups 136.46 mg/dl (Figure 4).

Effect of *Leucas indica variety Nagalapuramiana* on pancreatic weights: There was a remarkable reduction in the pancreatic weights in diabetic control rats (HFD+STZ) diverged from non-diabetic control rats. Roughly 1.48-fold abatement in the pancreatic weight was found in diabetic control rats. All the three doses of extracts conveyed an example of expanded pancreatic weight doses dependently (Figure 5). Noticeably, high dose of extracts conveyed around 1.29-fold, low dose 1.03-fold, mid dose 1.10-fold and metformin 1.43 fold recovery of pancreatic tissue mass with net pancreatic mass of 14 fold lesser than that of normal control rats.

Effect of *Leucas indica variety Nagalapuramiana* extract on plasma lipid profiles: The plasma triglyceride and total cholesterol levels were seen to be surprisingly increased in HFD+STZ control rats compared with standard chow diet fed control rats. There was 2.05 and 2.47fold addition in the triglyceride and total cholesterol levels in HFD+STZ rats appeared differently in relation to normal control rats. Following a month of treatment with plant extracts achieved dose dependant decrease in the triglyceride levels, different doses of plant extracts low, mid and high doses like, 10 mg/dl, 30 mg/dl and 100 mg/dl produces, low dose 1.04 fold, mid dose 1.32 fold and high dose extract showed 1.62 fold it is almost near to standard drug metformin 1.74 fold (Figure 6). Similarly, the total cholesterol levels were decreased in low dose 1.19-fold, mid dose 1.35-fold and high doses 1.85-fold of extracts treated rats appeared differently in relation to untreated diabetic control rats (Figure 7). The high dose (1.85-fold) extract treated rats showed lipid profiles which resembles close to metformin treated rats 2.09-fold.

Effect of extract on pancreatic histology: The Hematoxylin and Eosin (H&E) staining showed on pancreatic tissues clearly indicated degenerate and inflamed pancreatic histological changes in diabetic

control pancreas with severe penetration of inflammatory cells into pancreatic tissues. Comparison with HFD+STZ treated pancreatic tissues; nondiabetic rats clearly reveals that normal pancreatic beta cell and acinar cell histological studies with no confirmation of beta cell degeneration and inflammation. In diabetic control groups, the pancreatic histology showed expanded ductular fibrosis close by increase of ductular epithelial cells. Treatment with different doses extracts was found to be dose dependent improvement of debilitated histological discoveries. In treatment groups, there was no evidence of pancreatic beta cell degeneration. Similar kind of unblemished and conventional histological discoveries were seen on standard drug metformin treated rats. The amount of pancreatic beta cells and the ordinary size of beta cell and pancreatic cell mass were extremely reduced in HFD+STZ animals contrasted to non-diabetic control pancreas. Treatment with extracts showed dynamic and dose dependent improvement in the pancreatic beta cell number and beta cell sizes (Figure 8).

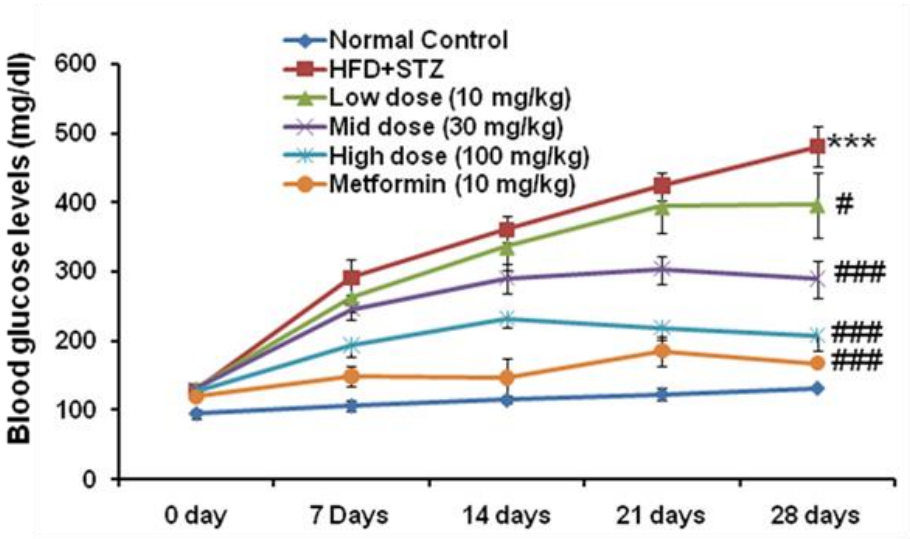

Figure 1: Effect of Oral administration of *Leucas indica variety Nagalapuramiana* extract on glucose levels evaluated in HFD+STZ induced type II diabetes model.

*Data was represented as mean±SEM (n=6).*** P<0.001 vs normal control group, # P<0.05 and ### P<0.001 vs HFD+STZ group

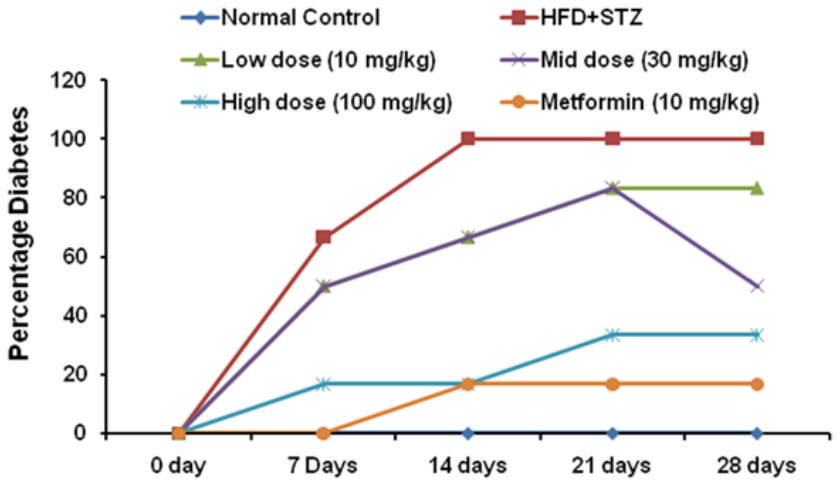

Figure 2: Effect of Oral administration of *Leucas indica variety Nagalapuramiana* extract on Diabetogenesis evaluated in HFD+STZ induced type II diabetes model.

*Data was represented as mean±SEM (n=6).

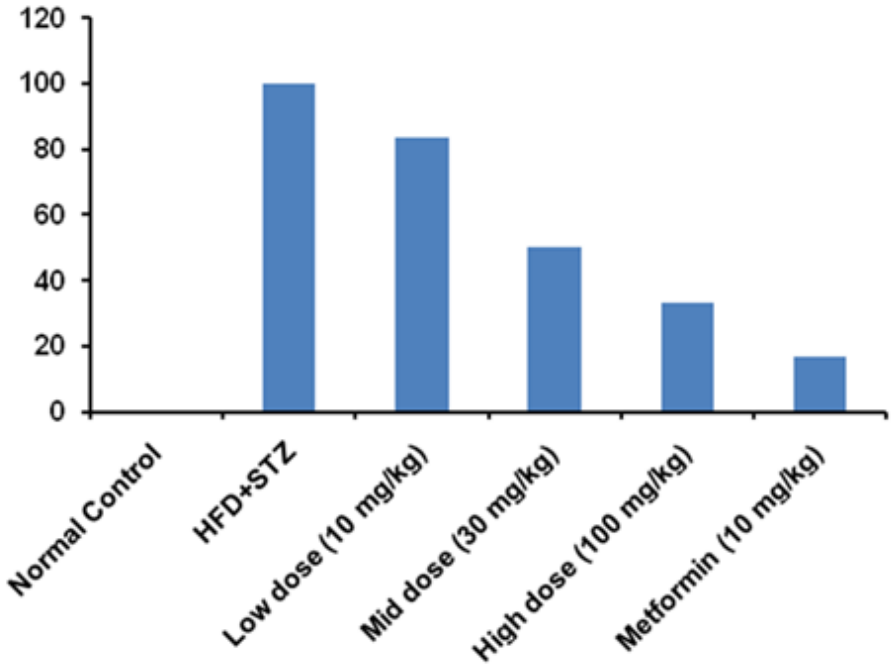

Figure 3: Effect of Oral administration of *Leucas indica variety Nagalapuramiana* extract on incidence of diabetes at the end of 28 days evaluated in HFD+STZ induced type II diabetes model.
*Data was represented as mean±SEM (n=6).

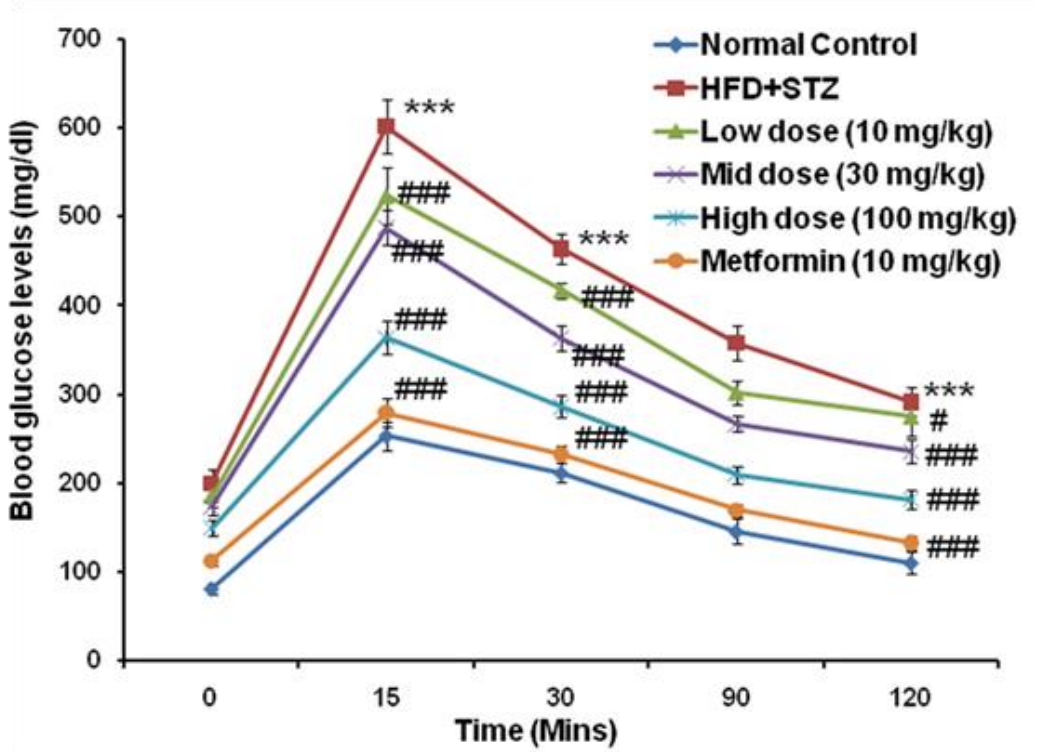

Figure 4: Effect of Oral administration of *Leucas indica variety Nagalapuramiana* extract on OGTT at the end of 120 minutes HFD+STZ induced type II diabetes model.
*Data was represented as mean±SEM (n=6).
*** P<0.001 vs normal control group, # P <0.05 and ### P<0.001 vs HFD+STZ group.

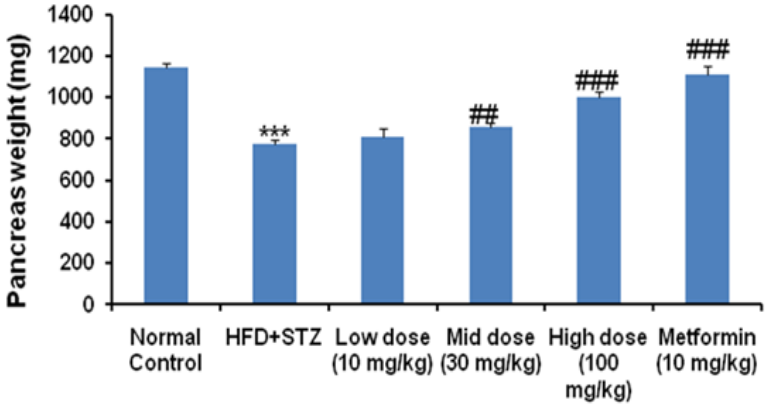

Figure 5: Effect of Oral administration of *Leucas indica variety Nagalapuramiana* extract on pancreatic weight at the end of 28 days evaluated in HFD+STZ induced type II diabetes model.

Data was represented as mean±SEM (n=6). *** P<0.001 vs normal control group, ## P <0.01 and ### P<0.001 vs HFD+STZ group.

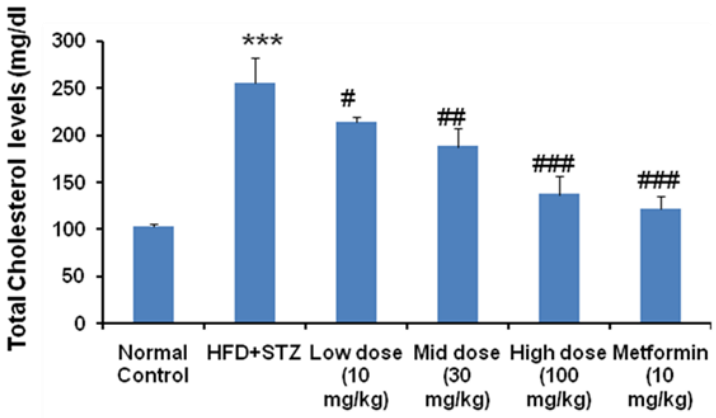

Figure 6: Effect of Oral administration of *Leucas indica variety Nagalapuramiana* extract on plasma total cholesterol levels at the end of 28 days evaluated in HFD+STZ induced type II diabetes model.

*Data was represented as mean±SEM (n=6). *** P<0.001 vs normal control group and # P <0.05, ## P<0.01 and ### P<0.001 vs HFD+STZ group.

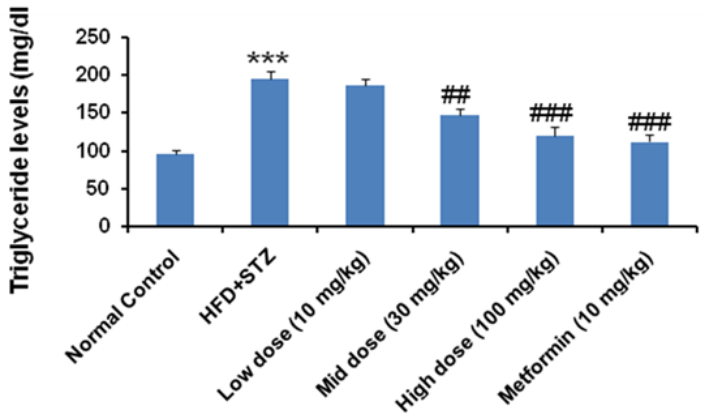

Figure 7: Effect of Oral administration of *Leucas indica variety Nagalapuramiana* extract on plasma triglyceride levels at the end of 28 days evaluated in HFD+STZ induced type II diabetes model.

*Data was represented as mean±SEM (n=6). *** P<0.001 vs normal control group, ## P<0.01 and ### P<0.001 vs HFD+STZ group.

DISCUSSION

In the present investigation we have made an effort to assess the protective role of *Leucas indica* extract in animal experimental model of type 2 diabetes. The active constituent *Leucas indica* was extracted productively by extraction and these extracts were described by GC-MS and other analytical techniques. The *Leucas indica* extract found to have promising antioxidant properties assessed by DPPH test.[14, 15, 16] In view of these *in vitro* antioxidant properties, the pancreatic beta cell protective role of *Leucas indica* was assessed in HFD+STZ induced type 2 diabetes model. The HFD+STZ model one of a kind nonhereditary animal model which is broadly utilized type 2 diabetes model for pharmacological screening. Once the hyperinsulinemia condition was seen in HFD nourished animals, the pancreatic beta cells are under extreme pressure conditions to deliver more elevated levels of insulin to keep up blood glucose levels [17]. In such pressure conditions, the low portion of STZ (35 mg/kg) can cause progressive beta cell injury which may cause the human type 2 diabetic condition.

In our model likewise we have seen serious injury to pancreatic beta cells within one week by post administration of STZ, however the portion of STZ is low, and it caused broad pancreatic beta cell injury because of co-existing metabolic disorder like condition [18]. Because of consistent beta cell injury, plasma glucose levels were gradually increased in HFD+STZ control animals. The plasma glucose levels were found to be considerably decreased in ethyl acetate extract treated animals, it is noticeable from the figure that leaves extract productively controlled the hyperglycemic conditions in time dependent and dose dependent way. Essentially, the percentage level of diabetes induction and diabetes incidences were diminished in ethyl acetate extract treated animals contrasted with untreated diabetic control animals.

The possible explanation for this protective role of pancreatic beta cell damage by active constituents present in leaf extracts antioxidant and anti-inflammatory effects [19, 20]. Since pancreatic beta cells are deteriorated or inured in HFD+STZ treated animals, the net pancreatic weight were gradually (33%) decreased. That implies the significant increases in pancreatic beta cell injury due to HFD and STZ it leads to beta cell crisis and serious hyperglycemia condition.

Curiously, constant oral induction of *Leucas indica* extract produced empowering beta cell ensuring hypoglycemia effect. These anti-hyperglycemic effects are equivalent to the standard anti-diabetic metformin treated animals. The information from glucose levels and diabetes rate unmistakably recommend that *Leucas indica* extract has protective role against HFD+STZ induced pancreatic injury. Since, leaves extracts are protecting the pancreatic beta cells; the OGTT likewise further exhibited improved glucose tolerance. The possible mechanism for anti-diabetic activity of *Leucas indica* is its antioxidant and anti-inflammatory properties [21, 22, 23]. In light of the biochemical profiles in pancreas and plasma biochemical parameters, it is clear that there is an increase in glucose levels which is for the most part because of damage of the pancreatic tissue.

Therefore, our extract may be compelling in the treatment of diabetic complications fundamentally vascular complications [24, 25]. Further, future work is justified to investigate these pharmacological actions. However, we have shown promising pancreatic defensive and anti-diabetic impacts of *Leucas indica* extracts, the doses utilized in the present investigations are in moderately higher range, in this manner, further examinations might be required to surpass dose related issues. Taken together our tests confirm that it is possible to treat type 2 diabetes. Along these lines, potential outcomes for clinical interpretation could be investigated for further investigation of such a fascinating plant extract with demonstrated health advantages.

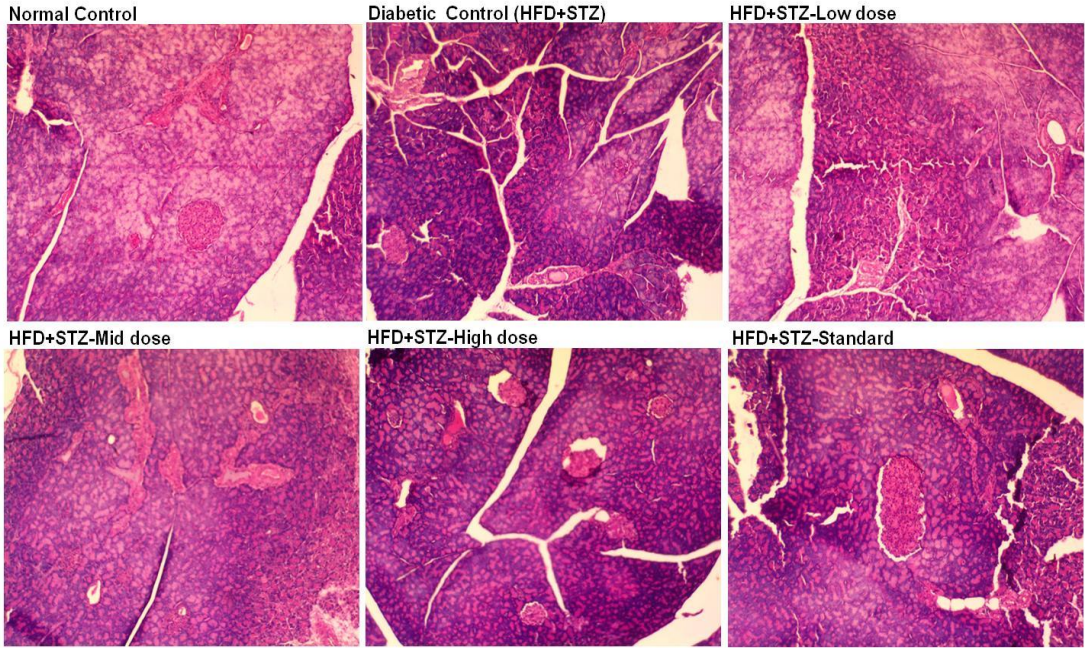

Figure 8: Effect of oral administration of *Leucas indica var Nagalapuramiana* extract on Histological features of pancreas (H&E staining) evaluated in HFD+STZ induced type II diabetes model.

Normal control: Glandular pancreas containing islets cells appeared normal collecting ducts in the glandular pancreas appeared normal,

Diabetic control (HFD+STZ): Severe degeneration of islets cells in glandular pancreas and Moderate to severe ductular fibrosis along with proliferation of ductular epithelial cells,

Low dose (HFD+STZ): Mild to moderate beta cell degeneration,

Mid dose (HFD+STZ): Mild to moderate degeneration of beta cells noticed in the islets of pancreas,

High dose (HFD+STZ): Glandular pancreas containing islets cells appeared normal

HFT+STZ with standard Metformin: Appeared normal Beta cells in the islets are appeared normal and no degeneration noticed in the

CONCLUSION

Our results clearly demonstrated significant beneficial effects of *Leucas indica var Nagalapuramiana* extracts in protecting pancreas from the high calorie diet and STZ induced deleterious effects. Based on all the biochemical parameter studies, it is clearly evident that ethylacetate fraction of *Leucas indica var Nagalapuramiana* produces highest protection against development of diabetes. More detailed molecular studies and isolation of active constituents from this plant may further provide vital information to explore for clinical studies.

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