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EVALUATION OF ANTIDIABETIC POTENTIAL OF METHANOLIC EXTRACT OF BENINCASA HISPIDA IN STREPTOZOTOCIN INDUCED DIABETIC RATS

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Keywords:

Diabetes mellitus, *Benincasa hispida*, streptozotocin, Hypoglycemic, Anti-diabetic

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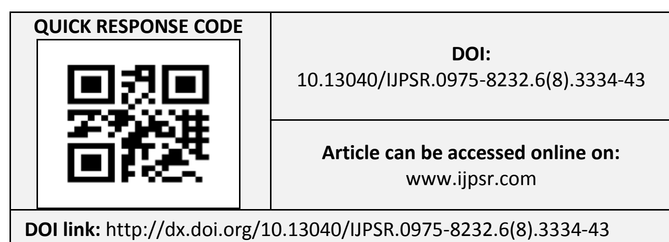
ABSTRACT: The number of patients with Diabetes mellitus is increasing rapidly both in developed and developing countries around the world. The existing medications especially synthetic drugs often fail to bring back normal glycemic control without complications. Numerous herbal medicines are widely explored as alternative medicine in diabetes. The objective of this work was to evaluate one such herbal extract of *Benincasa hispida* fruit for its anti-diabetic activity in experimentally induced diabetic rats. The extract at a dose of 200mg/kg/day and 400mg/kg/day was administered to streptozotocin induced diabetic animals for 15 consecutive days. Blood glucose levels, lipid profiles and body weight were measured for the evaluation of its anti-diabetic effect. The results of the study at both low and high dose of extract showed significant ($p<0.01$) decrease in blood glucose levels in diabetic rats. In addition, both the dose of extract also showed significant ($p<0.05$) decrease in serum triglyceride, VLDL levels, and an increase in HDL levels, though not significant. Only high dose of extract and glibenclamide treated group showed significant change in body weight and total cholesterol in the diabetic rats. Our study indicates that methanolic extract of *Benincasa hispida* has a promising effect in controlling blood glucose levels and also aid in counteracting the derangement of lipid profile, a major concern in diabetes mellitus.

INTRODUCTION: Diabetes mellitus is a chronic progressive metabolic disorder affecting every organ system and is associated with complications such as cardiovascular disease, retinopathy, neuropathy and nephropathy and is a leading cause of death and disability worldwide [1]. Its global prevalence was about 8% in 2011 and is predicted to rise to 10% by 2030. Nearly 80% of people with diabetes live in low and middle income countries [2]. In 2014 the global prevalence of diabetes was estimated to be 9% among adults aged 18+ years. In 2012, an estimated 1.5 million deaths were directly caused by diabetes.



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If these trends continue, by 2035 some 592 million people, or one adult in 10, will have diabetes[3]. India, the second most populous country of the world, has been severely affected by the global diabetes epidemic. As per the International Diabetes Federation (2013), approximately 50% of all people with diabetes live in just three countries: China (98.4 million), India (65.1 million) and the USA (24.4 million).

It is the fourth or fifth leading cause of death in most high-income countries and there is substantial evidence that it is changing into an epidemic in many low and middle-income countries [4]. Diabetes is certain to be one of the most challenging health problems in the 21st century [5]. Impaired insulin secretion (beta-cell), increased hepatic glucose production (liver), and decreased peripheral (muscle) glucose utilization constitute the

traditional primary defects responsible for the development and progression of diabetes mellitus[6].

Currently various synthetic chemical agents are available for control and treatment of diabetes but both total recovery and avoidance of complications from deranged lipid profile is a major concern till date. The treatment of diabetes mainly involves a sustained reduction in hyperglycemia by the use of biguanides, thiazolidinediones, sulfonylureas, D-phenylalanine and α-glucosidase inhibitors in addition to insulin. However, due to unwanted side effects the efficacies of these compounds are debatable and there is a demand for new compounds for the treatment of diabetes[7]. Hence there is always a need to evaluate newer and safer alternative molecules for the treatment of diabetes mellitus. One such path is to look for and scientifically study traditional plants and fruits used in South Asian countries for more than 1000 years. WHO expert committee on diabetes has recommended that traditional herbal medicines be further investigated[8].

Hence plants have been suggested as a rich, as yet unexplored source of potentially useful antidiabetic drugs. Many traditional herbal treatments for diabetes are used throughout the world. Plant drugs and herbal formulations are frequently considered to be less toxic and free from side effects than synthetic one. The anti-hyperglycemic effect of these plants are for their ability to restore the function of pancreatic tissues by increasing insulin output or inhibit the intestinal absorption of glucose or facilitation of metabolites in insulin dependent processes. Hence, treatment with herbal drugs has an effect on protecting β-cells and smoothing out fluctuation in glucose levels [9].

Benincasa hispida belongs to the *Cucurbitaceae* family used in ayurvedic system of medicines for various diseases like as dyspepsia, heart disease, vermifuge, and urinary disease. Certain scientific studies carried out reveal its anti inflammatory activity, diuretic activity, hypoglycemic, anti alzheimer's, anti-diarrheal, antioxidant, antiulcer, anti-obesity, antihistaminic and anti cancer property[10]. Prolonged insufficiency of insulin or its action lead to metabolic disturbances characterized by abnormal level of glucose, triglyceride and lipid levels in the blood and glycogen content in liver and muscle. Drugs that can completely or partially correct the disrupted mechanism should be able to show an alteration in the blood levels of these metabolites, which can be used as an indicator in its evaluation. Though there are many studies published to reveal the hypoglycemic activity of *Benincasa hispida,* only few studies have established its relation with restoring the derangement in lipid metabolism with histopathological examination of pancreas.

MATERIALS AND METHODS:

Plant Material: The fresh fruits of "*Benincasa hispida*" (Cucurbitaceae) were collected from local vegetable market. It was authenticated by Dr. K. P. Sreenath, Assistant Professor, Department of Botany, Bangalore University, Jhanabharti Campus, Bangalore, Karnataka, India.(Serial No – AMN 10)

Preparation of study extract:

Fresh fruit were cut into small piece and shade dried. They were then crushed to obtain a moderately coarse powder that was subjected to methanolic extraction process (courtesy Dr. Rajendran, Green Chem, Herbal Extracts & Formulation, Anekal Taluk, and Bangalore, India). The methanolic extract was collected & stored in desiccators for the study.

Chemicals:

All the chemicals and reagents used in the study are of analytical grade and molecular biology grade. Streptozotocin extract pure was purchased from Sisco Research Laboratories Pvt Ltd., Mumbai, India. Glibenclamide was obtained as gift samples from Embiotic, Bangalore, India. Reagents for estimation of glucose, total cholesterol, and triglycerides, HDL, LDL and VLDL were purchased from Pericugent, Thane, India.

Animals:

Male albino wistar rats weighing 150-200g were procured from Venkateshwara Enterprises, Bangalore. Animals were housed in polypropylene cages with paddy husk as bedding material. They were provided with standard pellet rodent diet (Amrut Laboratory animal feed, Sangli) and had free access to water. An acclimatization period of

fifteen days was allowed before the start of the experiment. All the procedures were performed in accordance with the guidelines issued by CPCSEA and the study protocol was approved by the institutional animal ethical committee vide certificate No. IAEC/NCP/72/13.

Induction of diabetes:
Diabetes was induced in rats by intraperitonial administration of 1% w/v solution of streptozotocin in 0.1M ice cold citrate buffer, at a dose of 40 mg/kg to overnight fasted healthy rats for 15 consecutive days. Animals were carefully monitored for sign of hypoglycaemia between 2nd hr to 10th hr and were administered 5% glucose solution orally whenever the symptoms appeared.

Methodology:
Forty male albino rats weighing in the range of 150 to 200 gm were administered the diabetogen streptozotocin to induce diabetes. Only animal exhibiting a fasting blood sugar level above 250mg/dl on the 5th day of administration were considered to be diabetic and used further in the experiment to represent diabetic rats. The diabetics rats were divided into four group of eight animal each. These groups were identified by numbering them from Group II to V. Sixteen non diabetic male albino rats were divided into two groups of eight each that were identified as Group I & VI.

Administration of the standard drug (glibenclamide 1 mg/kg per oral once daily for 15 days)[11] or two different doses of the extract (200 mg/kg per oral or 400 mg/kg per oral once daily for 15 days, based on toxicity studies done by Jayasree et al)[12] were carried out in accordance with the schedule as follows. Group II (Untreated diabetic rats, administered 0.5% carboxy methyl cellulose (CMC), at a dose of 0.5 ml/kg per oral once daily, for 15 days orally), Group III (glibenclamide treated diabetic rats), Group IV (low dose extract treated diabetic rats), Group V (high dose of extract treated diabetic rats), Group I (Non Diabetic Control rats, administered the plain suspension of 0.5% CMC at a dose of 0.5 ml/kg p.o once daily for 15 days orally) and Group VI (higher dose 400 mg/kg p.o extract treated non-diabetic rats).

Animals were subjected to the above treatment protocol for a period of fifteen days. They were allowed to have food and water *ad libitum.* After the fifteenth day of treatment the rats were fasted for a period of 18 hr and blood samples were collected by retro orbital puncture.

The samples were later used to determine the blood glucose levels and lipid profile. Individual body weight of rats at the start of the experiment and the final day before sacrificing was noted. Animals were then sacrificed, the pancreas excised out and kept immersed in 10% formalin. It was further processed for pathological examination.

Biochemical estimation: Blood samples drawn from each rat was collected in separate eppendrof tubes on the 16th day of the study. They were allowed to clot and centrifuged immediately to obtain clear serums that were stored at -80^{0}c or used immediately to carry out the estimations of glucose, triglyceride, total cholesterol, LDL, VLDL and HDL using a semi automatic Analyzer (Robonik prietest).

Histopathological analysis: The isolated pancreas was fixed using buffered neutral formalin solution that is strongly recommended for routine use. Pancreases were dehydrated using a serial concentration of ethyl alcohol ranging from 80-100% and then embedded into paraffin block. Sections of 5µm thickness were obtained using a microtome. These sections were transferred to glass slides and stained with hematoxylin and eosin to observe the histological pattern of the pancreatic tissue. The slides were then sent for microscopic analysis to a medical pathologist for histological observation and comments.

Statistical Analysis: The values obtained for each biochemical parameter and changes in body weight of the animal groups were subjected to column statistical analysis to obtain the mean ± S.E.M for the group. The differences were compared using one way analysis of variance (ANOVA) followed by Dunnett's test (Graph Pad Prism 5 for Windows, Version 5.03, U.S.A), p values<0.05 were considered as significant. The unpaired student t test was used to assess the level of significance associated between the two non diabetic groups.

RESULTS:

Biochemical parameters:

Administration of streptozotocin for 15 days resulted in an increase of fasting blood glucose (FBG), serum triglyceride (TGL), total cholesterol, low density lipoprotein (LDL), very low density lipoprotein (VLDL) and a decrease of fasting serum high density lipoprotein (HDL) levels in Group II (Untreated diabetic rats). Non-injected rats did not exhibit such a change in Group I (Non diabetic control rats). Difference between the two groups was highly significant ($p< 0.001$) for all above parameters except serum HDL levels which was moderately significant ($p< 0.05$).

Administration of glibenclamide , lower dose of the extract (200mg/kg) or the higher dose of the test extract (400mg/kg) orally for 15 days (Group III,IV,V) resulted in a corresponding decrease in fasting blood glucose (FBG), serum triglyceride (TGL), total cholesterol, LDL, VLDL and an increase of fasting serum HDL levels. The changes in FBG, TGL, and VLDL levels were significant ($p<0.05$) in above three groups in comparison to group II (untreated diabetic rats). The change in LDL level was not significant in all the three group (Low or High Dose extract treated diabetic rats & glibenclamide treated diabetic rats) compared to Group II (Untreated diabetic rats).

The difference in total cholesterol was significant ($p<0.05$) in Group III (glibenclamide extract treated diabetic rats) and in Group V (high dose extract treated diabetic rats), but not significant in Group IV (low dose extract treated diabetic rats) in comparison to group II (Untreated diabetic rats). Though there was some increase in HDL levels in all the three groups but not significant.

Oral administration of the higher dose of the extract to non diabetic rats resulted in a increase in fasting blood glucose (FBG) levels, total cholesterol, HDL levels, LDL levels and decrease in serum triglyceride (TGL) levels and serum VLDL levels in Group VI (high dose extract treated non-diabetic rats). These changes were not significant compared to Group I (Non Diabetic Control rats), refer **Table 1** & **2 and Fig. 1** to **6** below.

TABLE 1: EFFECT OF MEBH ON FASTING BLOOD GLUCOSE LEVEL AND BODY WEIGHT IN ANIMAL MODEL

Treatment N=8	Fasting Blood Glucose level		Change in body weight	
	Mean±SEM	**%Reduction in blood glucose**	**Mean±SEM**	**% Change**
Non-diabetic control (Group I)	89.92±5.60	-	0.24±0.02	-
Untreated Diabetic rats (Gp II)	476.9±55.32[a,***]	↑ 530	-0.27±0.02[,a***]	↓ 113
Glibenclamide (1mg/kg b.w.) treated diabetic rats (Gp III)	177.5±10.60[b,**]	↓ 62.78	-0.12±0.00[b,**]	↓ 44.87
Low dose MEBH (200mg/kg b.w) treated Diabetic rats (Gp IV)	232.3±12.12[b,**]	↓ 51.28	-0.1908±0.0[b,ns]	↓ 68.38
High dose MEBH (400mg/kg b.w) treated Diabetic rats (Gp V)	207.0±16.33[b,**]	↓56.59	-0.1253±0.0[b,**]	↓ 45.56
High dose MEBH (400mg/kg b.w) treated Non-Diabetic rats (Gp VI)	101.8±10.56[a,ns]	↑ 13.20	0.2750±0.0[a,ns]	↑ 111.4

[a] when compared with Normal Control; [b]when compared with Diabetic Control, ; [ns]not significant ** $p < 0.01$; *** $p < 0.001$. % Reduction in FBG = (C_{DT} / C_{DC} -1) X 100, Where, C_{DC} – Average blood glucose conc. of the diabetic control group. C_{DT} - Average blood glucose conc. of the drug treated group. % Change in body weight = V_t /V_{ut} X 100. MEBH**:** Methanolic Extract of *Benincasa Hispida.*

TABLE 2: EFFECT OF MEBH ON LIPID PROFILE IN ANIMAL MODEL

Groups with treatment N=8	TGL		Total cholesterol		HDL		LDL		VLDL	
	Mean ± SEM	**%Reduction**	**Mean ± SEM**	**%Reduction**	**Mean ± SEM**	**%Reduction**	**Mean ± SEM**	**%Reduction**	**Mean ± SEM**	**%Reduction**
Non-diabetic control (Gp I)	91.44 ± 9.07	-	55.76 ± 2.83	-	25.63 ± 1.76	-	12.38 ± 4.517	-	18.28 ± 1.816	-
Untreated Diabetic rats (Gp II)	276.6 ± 38.81[a,***]	↑302	122.7 ± 5.88[a,***]	↑220	18.49 ± 1.60[a,**]	↑72	49.02 ± 5.69[a,***]	395↑	55.32 ± 7.761[a,***]	↑302

Glibenclamide (1mg/kg b.w.) treated diabetic rats (Gp III)	129.7 ± 5.95^{b,**}	↓53.11	90.09 ± 3.19^{b,**}	↓ 25.92	25.20 ± 2.66^{b,ns}	↑ 37.90	38.95 ± 3.87^{b,ns}	↓ 20.55	25.94 ± 1.19^{b,**}	↓ 53.11
Low dose MEBH (200mg/kg b.w) treated Diabetic rats (Gp IV)	180.8 ± 8.30^{b,**}	↓34.63	109.6 ± 9.91^{b,ns}	↓ 10.68	21.55 ± 2.17^{b,ns}	↑ 16.50	51.86 ± 9.13^{b,ns}	↓ 5.70	36.15 ± 1.66^{b,**}	↓ 34.66
High dose MEBH (400mg/kg b.w) treated Diabetic rats (Gp V)	122.6 ± 4.51^{b,**}	↓55.66	93.37 ± 3.77^{b,*}	↓ 23.42	24.90 ± 0.44^{b,ns}	↑ 34.60	43.92 ± 3.93^{b,ns}	↓ 10.41	24.67 ± 0.96^{b,**}	↓ 55.41
High dose MEBH (400mg/kg b.w) treated Non-Diabetic rats (Gp VI)	78.41 ± 11.93^{a,ns}	↓ 14.24	59.73 ± 1.65^{a,ns}	↑ 7.10	27.49 ± 1.65^{a,ns}	↑ 7.20	15.75 ± 2.42^{a,ns}	↑ 27.70	15.68 ± 2.38^{a,ns}	↓ 14.22

^{a} when compared with Normal Control; ^{b}when compared with Diabetic Control, ^{ns}not significant, * $p < 0.05$, ** $p < 0.01$; *** $p < 0.001$. % Reduction in lipid profile = (C_{DT} / C_{DC} -1) X 100, Where, C_{DC} – Average blood lipid conc of the diabetic control group. C_{DT} - Average blood lipid conc of the drug treated group. MEBH: Methanolic Extract of *Benincasa Hispida.*

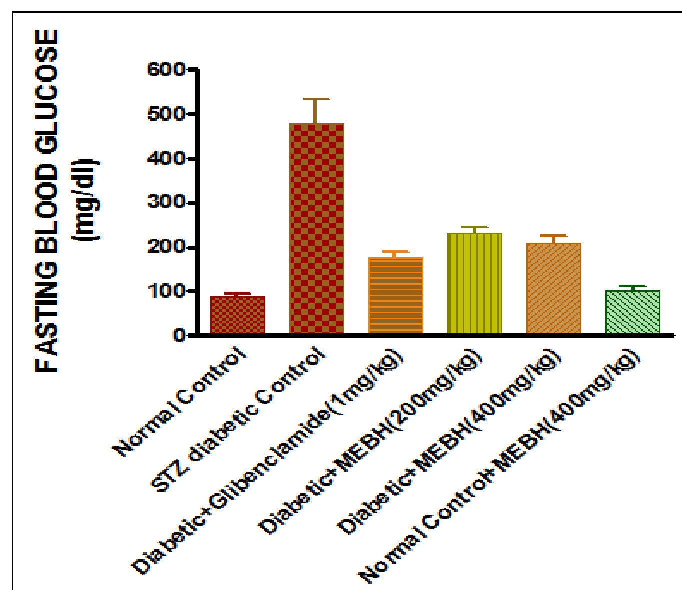

FIG. 1: EFFECT OF METHANOLIC EXTRACT OF *BENINCASA HISPIDA* ON FASTING SERUM GLUCOSE LEVEL IN STZ INDUCED DIABETIC ANIMAL MODEL

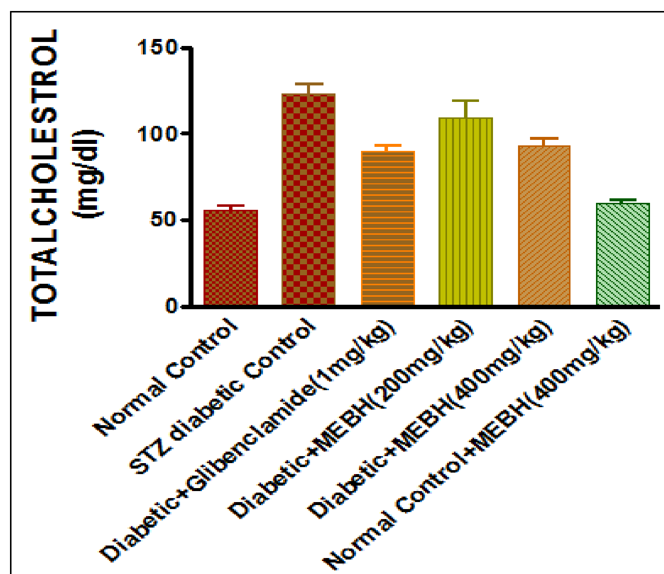

FIG. 1: EFFECT OF METHANOLIC EXTRACT OF *BENINCASA HISPIDA* ON FASTING SERUM TOTAL CHOLESTROL LEVEL IN STZ INDUCED DIABETIC ANIMAL MODEL

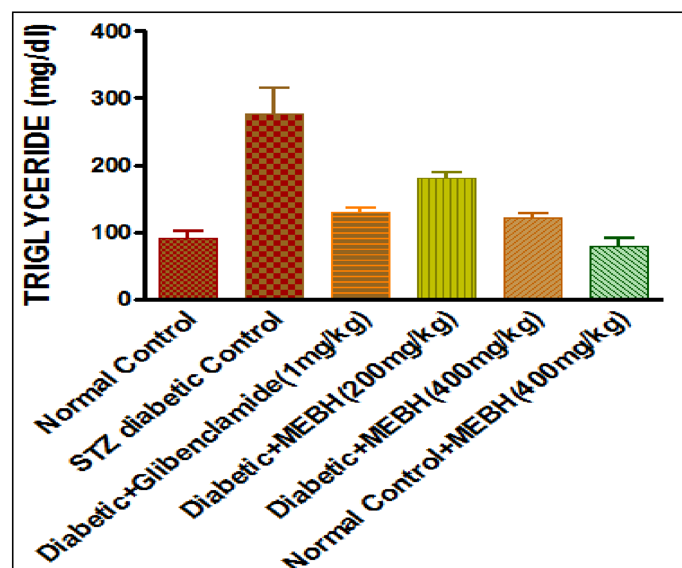

FIG. 2: EFFECT OF METHANOLIC EXTRACT OF *BENINCASA HISPIDA* ON FASTING SERUM TRIGLYCERIDES LEVEL IN STZ INDUCED DIABETIC ANIMAL MODEL

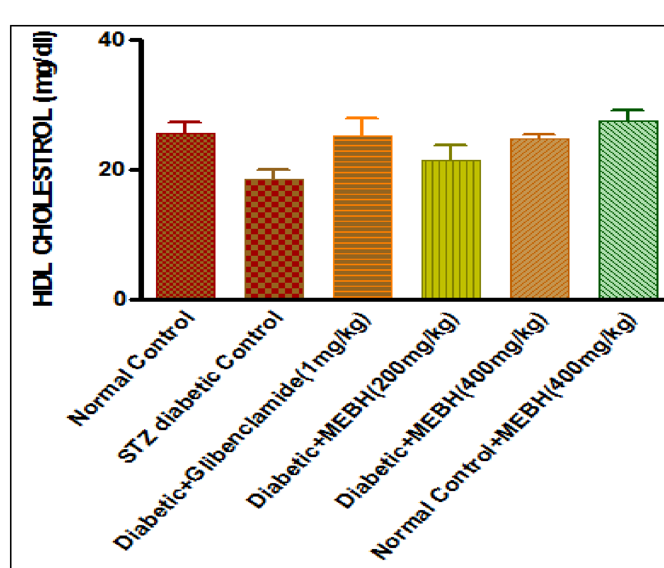

FIG. 1: EFFECT OF METHANOLIC EXTRACT OF *BENINCASA HISPIDA* ON FASTING SERUM HDL CHOLESTROL LEVEL IN STZ INDUCED DIABETIC ANIMAL MODEL

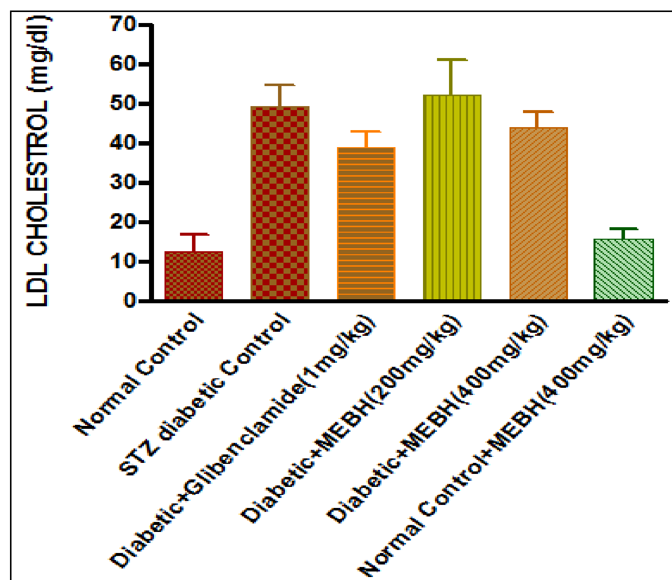

FIG. 5: EFFECT OF METHANOLIC EXTRACT OF *BENINCASA HISPIDA* ON FASTING SERUM LDL CHOLESTROL LEVEL IN STZ INDUCED DIABETIC ANIMAL MODEL

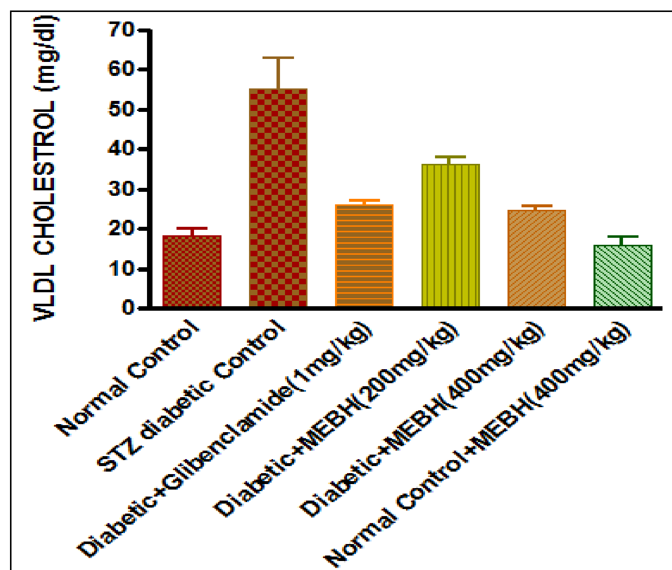

FIG. 6: EFFECT OF METHANOLIC EXTRACT OF *BENINCASA HISPIDA* ON FASTING SERUM VLDL CHOLESTROL LEVEL IN STZ INDUCED DIABETIC ANIMAL MODEL

Body weight: The results of change in body weight observed during the experimental period for the different groups are as indicated in **Table 1**. Administration of streptozotocin resulted in drastic loss of body weight in Group II (untreated diabetic rats), where as in Group I (non diabetic control rats) did not exhibit such a change. The difference between two groups was highly significant ($p< 0.001$). Administration of glibenclamide, lower dose of the extract (200mg/kg) or the higher dose of the test extract (400mg/kg) orally (Group III, IV, V) resulted in loss of body weight. The changes observed were moderately significant ($p<0.01$) in Group III (glibenclimide treated diabetic rats) and in Group V (high dose extract treated diabetic rats), whereas not significant in Group IV (low dose extract treated diabetic rats) in comparison to Group II (untreated diabetic rats).

Oral administration of the higher dose of extract to non diabetic rats resulted in increase in body weight in Group VI (high dose extract treated Non diabetic rats). This change was not significant compared to Group I (non diabetic control rats).

Histopathological observation of Pancreas: Untreated non-diabetic rats (Group-I) and high dose treated non diabetic rats (Group VI) revealed large number of light staining islet of langerhans with normal pancreas architecture. Whereas the untreated diabetic group (Group II) showed a reduction in number of islets which constituted lesser beta cells. Glibenclamide, low dose extract & high dose extract treated groups showed an increase in number of islets with normal pancreatic architecture with adequate beta cells. Refer **Fig. 7-18** below.

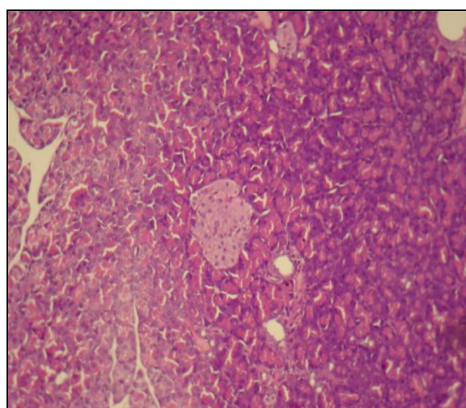

FIG.7: [H&E, X100]

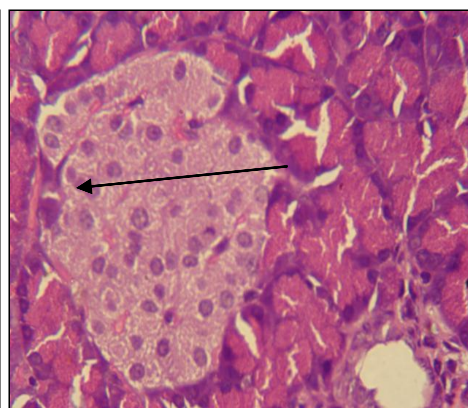

FIG.8: [H&E, X400]

Group I (Non-Diabetic control rats): Section studied shows pancreatic lobules separated by connective tissue septa. Most of the lobules show small, round, light staining islets of Langerhans. The center of islet cells consist of β-cells (60%), while the periphery comprises of α-cells (35%).

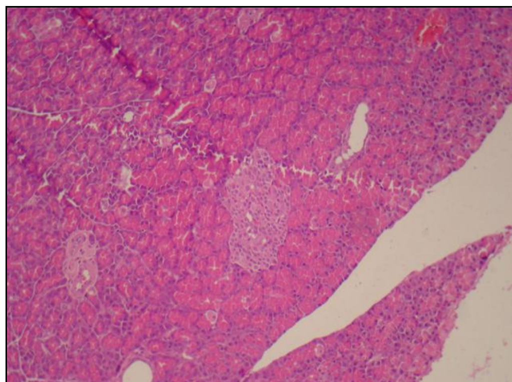

FIG.9: [H&E, X100]

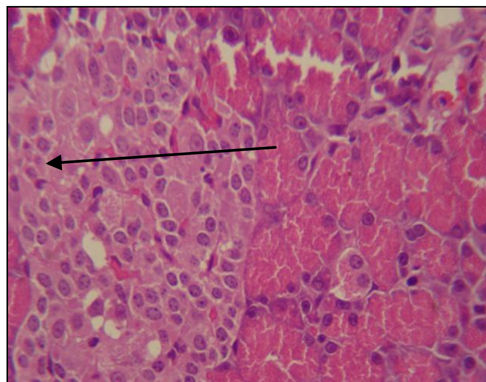

FIG.10: [H&E, X400]

Group II (Untreated Diabetic rats): Section studies show pancreatic lobules separated by connective tissue septa. The number of islets appears reduced in number. The center of islet cells consists of quantitative decrease in β-cells (30%) having basophilic granules, while the periphery comprises of large α-cells (65%) having esinophilic granules. This refers degenerated β-cells.

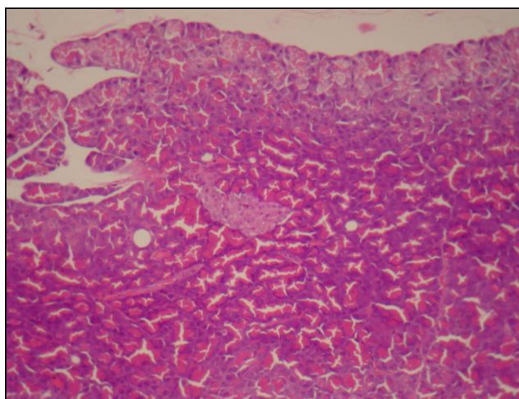

FIG.11 [H&E, X100]

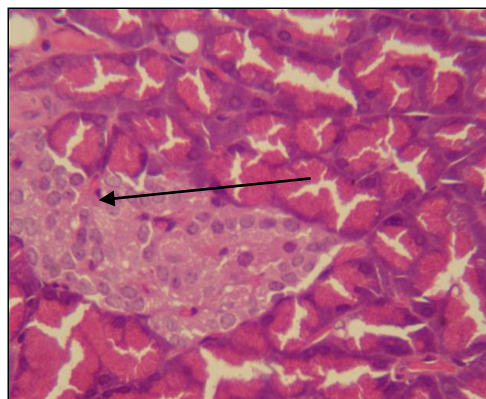

FIG.12 [H&E, X100]

Group III (Glibenclamide treated diabetic rats): Section studies show pancreatic lobules separated by connective tissue septa. The number of islets appears reduced in number. The center of islet cells consists of quantitative increase in β-cells (75%) having basophilic granules, while the periphery comprises of large α-cells (20%) having esinophilic granules.

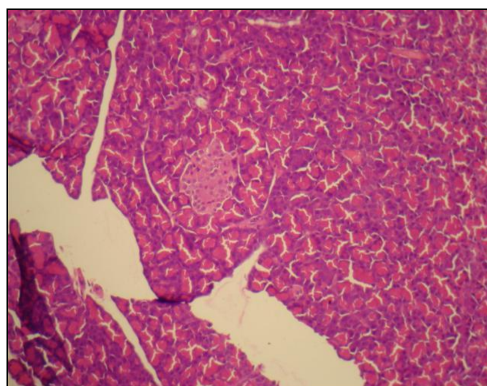

FIG.13 [H&E, 100]

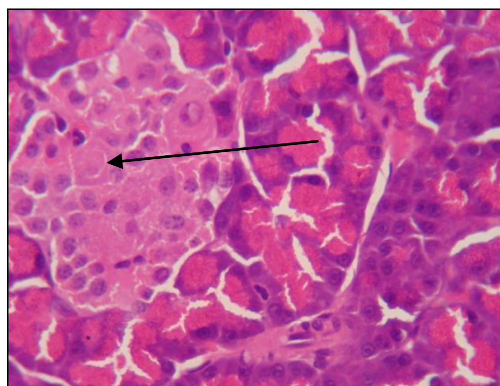

FIG.14 [H&E, X400]

Group IV (Low dose extract treated diabetic rats): Section studies show pancreatic lobules separated by connective tissue septa. The number of islets appears reduced in number. The center of islet cells consists of quantitative increase in β-cells (65%) having basophilic granules, while the periphery comprises of large α-cells (30%) having esinophilic granules.

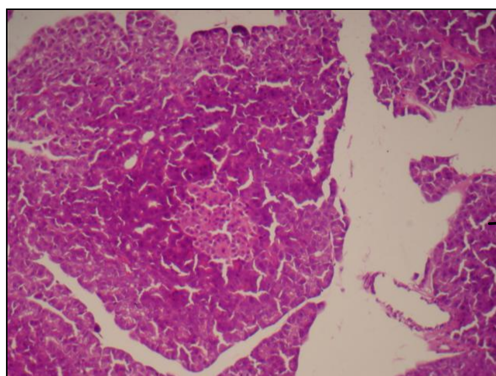

FIG.15 [H&E, X100]

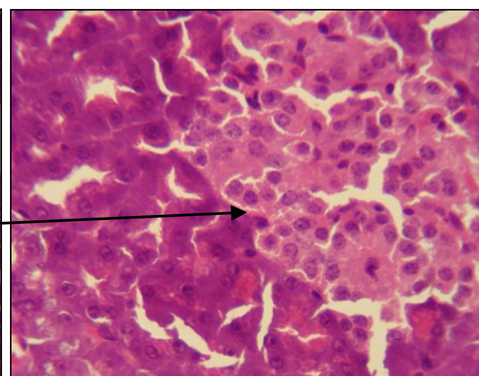

FIG.16 [H&E, X400]

Group V (High dose extract treated diabetic rats): Section studies show pancreatic lobules separated by connective tissue septa. The number of islets appears reduced in number. The center of islet cells consists of quantitative increase in β-cells (70%) having basophilic granules, while the periphery comprises of large α-cells (25%) having esinophilic granules.

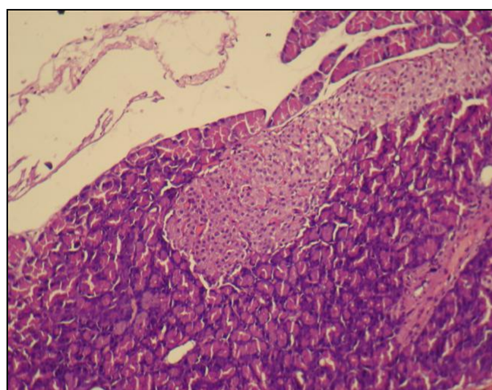

FIG.17 [H&E, X100]

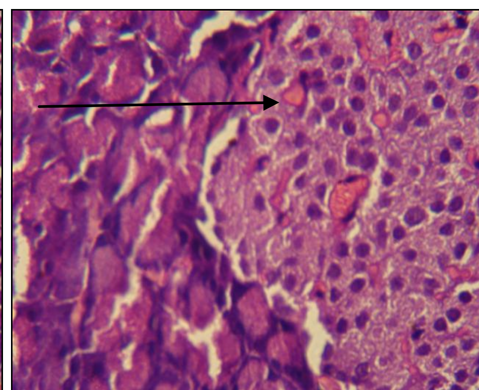

FIG.18 [H&E, X400]

Group VI (High dose extract treated non-diabetic rats): Section studied shows pancreatic lobules separated by connective tissue septa. Most of the lobules show small, round, light staining islets of Langerhans. The center of islet cells consist of β-cells (60%), while the periphery comprises of α-cells (35%).

DISCUSSION: Diabetes mellitus is the most common endocrine disease in the world. The World Health Organization estimates that the disease is responsible for about 5% of all deaths globally each year, a figure that is projected to increase by 50% within a decade. Diabetes mellitus is easily diagnosed by the characteristic chronic elevation in blood glucose concentration, but is in fact merely an umbrella diagnosis with several disease subtypes[13]. Though there have been a flood of molecules and research for new ones for treatment of diabetes, still the problem continues to arise in the world. It is a huge burdens on the economy especially the developing countries with exponential growth, aging population and drastic lifestyle changes. Traditional medicine is still the lifeline of vast majority of people in South East Asian countries. The major hindrance is lack of scientific studies and purity of the extract.

Off late there has been plethora of literature on hypoglycemic activity of traditional medicines like *Acacia Arabica, Benincasa hispida, Tinisporia cordifolia, Jatropa curcas, Azadirachta Indica* and

Ocimum sanctum. Most of the studies published on these molecules aim to reduce the blood glucose levels but neglect the altered lipid profile, which plays a vital role in long term complications of diabetes. In view of available literature on *Benincasa hispida,* an attempt was made to evaluate the hypoglycemic activity of methanolic extract of this molecule and establish a correlation with its positive effect in reversal of derangement of lipid profile.

As mentioned in the results, at both low and high dose of methanolic extract of *Benincasa hispida* showed significant ($p<0.01$) decrease in fasting serum glucose levels when compared with untreated streptozotocin induced diabetic rats. Similar results were observed in studies by Raju N patil et al, at dosage of 250 and 500 mg/kg body weight[14]. A study by Jayasree et al at dosage of 200 and 400 mg/kg body weight showed significant hypoglycemic activity in male wistar rats[15]. A study by Mohana Rupa et al evaluated graded doses of aqueous extract of test drug (*Benincasa Hispida*) i.e., 50mg/kg, 100mg/kg and 200mg/kg respectively. The extracts showed dose-dependent significant ($P < 0.05$) reduction in the blood glucose levels, when compared with that of the control [9].

In this study both low and high dose of extract showed significant ($p<0.05$) decrease in serum triglyceride and VLDL level when compared with untreated streptozotocin induced diabetic rats. Though there was some increase in the HDL levels, it was not significant ($p>0.05$) in low dose extract, high dose extract and glibenclamide treated groups, the reason for which could not be ascertained. A similar reduction of fat was reported by Ming Gu et al, the study concluded that their results provide evidence that extract of wax guard peel *Benincasa hispida* played a role in ameliorating metabolic disorders in high-fat diet fed mice[16].

There is a definitive role for oxidative stress in development and complications of diabetes. Oxidative stress due to hyperglycemia causes cellular injury, over production of mitochondrial superoxide in endothelial cells. Chronic hyperglycemia and oxidative stress have multiple deleterious effect on the function of vascular, retinal and renal tissues[17]. Apart from anti-diabetic activity, *Binincasa hispida* has also proven to have antioxidant property, a study by Sheela K et al suggested that the herbal plants like *Binincasa hispida* and *Andrographis paniculata* posses the hypoglycemic effect or anti-diabetic effect and antioxidant activities, which might be helpful in preventing or slowing the progress of diabetes[18].

Administration of glibenclimide, lower dose and high dose of the extract resulted in a corresponding loss of body weight in diabetic rats. In comparison to Group II (untreated diabetic rats) the changes in body weight observed were significant in glibenclamide and high dose extract treated diabetic rats ($p<0.01$) whereas not significant for Group IV(low dose extract treated diabetic tats). A study by Sheela K et al relived a slight increase in body weight and protein in streptozotocin induced diabetic rats[18]. In the current study both low dose and high dose extract rats (Group IV & V) revealed pancreas with an increase in number of islets with normal pancreatic architecture with adequate beta cells. Thus establishing the role of *Benincasa Hispida* in restoring the architecture of pancreas in terms of increase in number of islet cells with adequate beta cells to secrete insulin.

The above finding indicate that the methanolic extract of *Benincasa hispida* can be effectively used in diabetes mellitus. Our studies suggest that methanolic extract of *Benincasa hispida* is effective in bringing back glycemic and lipemic levels to normal in streptozotocin induced hyperglycemia, hypercholesterolemia and hypertriglyceridemia in albino rats. The probable mechanism involved might be antioxidant potential of *Benincasa hispida* that prevent damage to Beta cells by free radicals. Further studies into these aspects might reveal the actual mechanisms involved in anti-diabetic activity of methanolic extract of *Benincasa hispida.*

CONCLUSION: Our study suggests that herbal plant extract *Benincasa hispida* posess hypoglycemic activity that might be helpful in preventing progression of diabetes. In addition there was good correlation in correcting the lipid derangement commonly seen in diabetic people leading to long term morbidity and mortality. Since many antidiabetic drugs do not correct

dyslipidemia, the observed hypolipidemic effect of this plant extract in diabetic rats makes *Benincasa hispida* quite important. Further investigations are needed to elucidate the exact mechanism of action, particularly the bioactivity-guided fractionation, isolation-identification and enzymatic study of constituents of the plant extract responsible for the observed pharmacologic activities.

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