IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)
e-ISSN: 2279-0853, p-ISSN: 2279-0861.Volume 13, Issue 12 Ver. V (Dec. 2014), PP 118-125
www.iosrjournals.org

Evaluation of Antidiabetic Potential of Methanolic Extract of Benincasa Hispida in Dexamethasone Induced Diabetic Rats

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Abstract: *Diabetes mellitus is one of the major public health problems throughout the world. Current therapies 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 dexamethasone induced insulin resistant animals for 10 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, total cholesterol, VLDL levels, and an increase in HDL levels, though not significant. Only high dose of extract showed significant ($p<0.01$) increase in body weight 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.*

Keywords: *Diabetes mellitus, Benincasa hispida, Dexamethasone, Hypoglycemic, Anti-diabetic*

I. Introduction

Diabetes is a condition primarily defined by the level of hyperglycaemia giving rise to the risk of microvascular damage (retinopathy, nephropathy and neuropathy). It is associated with reduced life expectancy, significant morbidity due to specific diabetes related microvascular complications, increased risk of macrovascular complications (ischaemic heart disease, stroke and peripheral vascular disease), and diminished quality of life[1]. Worldwide 347 million people suffer from diabetes and WHO projects it as the seventh leading cause of death by 2030[2,3]. In 2012, an estimated 1.5 million deaths were directly caused by diabetes and more than 80% of these death occurred in low and middle income countries[4,5]. 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 type 2 diabetes mellitus[6].

Currently available therapies and drugs only aim to decrease blood glucose levels but do not take care of the long term complications mainly due to altered lipid metabolism. In addition the available synthetic drugs are not devoid of complications, as preclinical in vivo studies and limited human data suggest a possible increased risk of bladder cancer with pioglitazone therapy[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 been 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]. Some of these herbal medicines are Acacia Arabica (Momosaceae), Benincasa hispida (Cucurbitaceae) , Tinisporia cordifolia(Menispermaceae), Jatropa curcas (Euphorbiaceae) and Ocimum sanctum Linn which are traditionally used for the treatment of diabetes[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, hypoglycaemic, Anti Alzheimer's, antidiarrheal, antioxidant, antiulcer, antiobesity, 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 and architecture of liver parenchyma.

II. Materials And Methods

2.1) 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)

2.2) 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, Bangalore, India). The methenolic extract was collected & stored in desiccator for the study.

2.3) Chemicals: All the chemicals and reagents used in the study are of analytical grade and molecular biology grade. Dexamethasone sodium phosphate (DEXONA) was purchased from Zydus Cadila, India. Pioglitazone was obtained as gift samples from Dr. Reddy's Laboratories Limited, Hyderabad, India. Reagents for estimation of glucose, total cholesterol, triglycerides, HDL, LDL and VLDL were purchased from Pericugent, Thane, India.

2.4) 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.

2.5) Induction Of Insulin Resistant Diabetes: Insulin resistance diabetes was induced in rats by the subcutaneous administration of dexamethasone sodium phosphate 5mg/kg body weight once daily over a period of 10 days. Animals were carefully monitored for sign of hypoglycaemia between 2^{nd} hr to 10^{th} hr and were administered 5% glucose solution orally whenever the symptoms appeared.

2.6) Methodology: Forty male albino rats weighing in the range of 150 to 200 gm were administered the diabetogen dexamethasone to induce insulin resistant diabetes. Only animal exhibiting a fasting blood sugar level above 250mg/dl on the 5^{th} 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 (pioglitazone 10 mg/kg once daily for ten days) or two different doses of the extract (200 mg/kg or 400 mg/ kg once daily for ten days, based on toxicity studies done by Jayasree et al)[11] were carried out in accordance with the schedule as follows. Group II (Untreated diabetic rats, administered 0.5% carboxy methyl cellolose (CMC), at a dose of 0.5 ml/kg once daily, for 10 days orally), Group III (pioglitazone 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 once daily for 10 days orally) and Group VI (higher dose extract treated non-diabetic rats).

Animals were subjected to the above treatment protocol for a period of ten days. They were allowed to have food and water ad libitum. After the tenth 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 liver excised out and kept immersed in 10% formalin. It was further processed for pathological examination.

2.7) Biochemical Estimation: Blood samples drawn from each rat was collected in separate eppendrof tubes on the 11^{th} day of the study. They were allowed to clot and centrifuged immediately to obtain clear serums that were stored at -80^0c or used immediately to carry out the estimations of glucose, triglyceride, total cholesterol, LDL, VLDL and HDL using a semi automatic Analyzer (Robonik prietest).

2.8) Histopathological Analysis: The isolated livers were fixed using Carnoy's fixative solution that is well known for its quick penetration, excellent nuclear fixation, glycogen preservation and reduced hardening of the tissue when exposed to alcohol. Isolated livers were then 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 hepatic tissue. The slides were then sent for microscopic analysis to a medical pathologist for histological observation and comments.

2.8) 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.

III. Results

3.1) Biochemical Parameters: Administration of dexamethasone s.c. for 10 days resulted in a 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 mildly significant ($p< 0.05$).

Administration of pioglitazone , lower dose of the extract (200mg/kg) or the higher dose of the test extract (400mg/kg) orally for 10 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, total cholesterol and VLDL levels were moderately significant ($p<0.01$) in above three groups in comparison to group II (untreated diabetic rats). The change in LDL level was not significant in extract treated group (Low & High Dose) where as in Group III (pioglitazone treated diabetic rats) it was significant. 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 No.1: Effect of MEBH on fasting blood glucose level and body weight in animal model

		Fasting Blood Glucose level		Change in body weight	
Group N=8	**Treatment**	**Mean±SEM**	**%Reduction in blood glucose**	**Mean±SEM**	**% Change**
I	Non-diabetic control	89.92±5.60		0.24±0.02	
II	DEXA induced diabetic Control	$265.3±9.00^{a,***}$	↑ 295	$-0.27±0.01^{a,***}$	↓ 109
III	Diabetic group treated with 10mg/kg b.w. pioglitazone	$113.5±18.31^{b,**}$	↓ 42.78	$-0.13±0.00^{b,**}$	↓ 49.26
IV	Diabetic group treated with 200mg/kg b.w of MEBH	$139.3±17.98^{b,**}$	↓52.50	$-0.26±0.01^{b,ns}$	↓ 97.85
V	Diabetic group treated with 400mg/kg b.w of MEBH	$125.1±7.97^{b,**}$	↓ 47.15	$-0.19±0.02^{b,**}$	↓ 71.03
VI	Non diabetic treated with 400mg/kg b.w of MEBH	$101.8±10.56^{a,ns}$	↑ 13.20	$0.27±0.03^{a,ns}$	↑ 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 No.2: Effect of MEBH on lipid profile in animal model

	TGL		Total cholesterol		HDL		LDL		VLDL	
Groups with treatment N=8	**Mean ± SEM**	**% Reduction**	**Mean ± SEM**	**% Reduction**	**Mean ± SEM**	**% Reduction**	**Mean ± SEM**	**% Reduction**	**Mean ± SEM**	**% Reduction**
Non-diabetic control rats (Gp I)	91.44 ± 9.07		55.76 ± 2.83		25.63 ± 1.76		12.38 ± 4.517		18.28 ± 1.81	
Untreated Diabetic rats (Gp II)	248.7 ± $12.52^{a,***}$	↑271	129.9 ± $7.22^{a,***}$	↑232	19.45 ± $0.12^{a,*}$	↓ 75.88	60.79 ± $6.174^{a,***}$	↑491	50.99 ± $3.35^{a,***}$	↑278
Pioglitazone (10mg/kg b.w) treated diabetic rats (Gp III)	110.8 ± $2.16^{b,**}$	↓ 55.45	78.86 ± $10.28^{b,**}$	↓ 39.3	24.71 ± $4.19^{b,ns}$	↑ 27.0	31.97 ± $6.797^{b,*}$	↓ 47.41	22.19 ± $0.431^{b,**}$	↓ 56.49
Low dose MEBH (200mg/kg b.w) treated Diabetic rats (Gp IV)	180.5 ± $7.44^{b,**}$	↓ 27.48	98.88 ± $6.96^{b,*}$	↓ 23.88	21.00 ± $1.63^{b,ns}$	↑ 7.9	41.79 ± $7.098^{b,ns}$	↓ 31.26	36.09 ± $1.48^{b,**}$	↓ 29.33
High dose MEBH (400mg/kg b.w) treated Diabetic rats (Gp V)	133.6 ± $8.38^{b,**}$	↓ 46.29	91.89 ± $4.46^{b,**}$	↓ 29.27	22.12 ± $2.92^{b,ns}$	↑ 13.7	43.06 ± $7.171^{b,ns}$	↓ 29.17	26.71 ± $1.67^{b,**}$	↓ 47.62
High dose MEBH (400mg/kg b.w) treated Non-Diabetic rats (Gp VI)	78.41 ± $11.9^{a,ns}$	↓ 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.

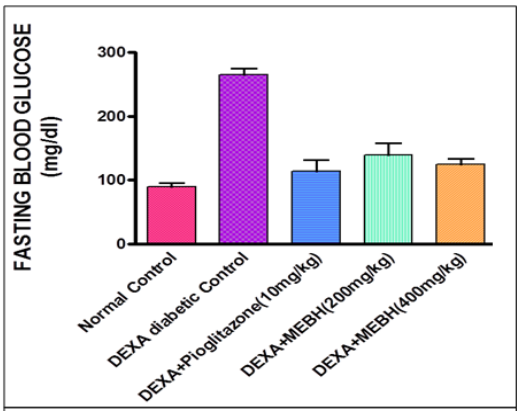

Figure 1: Effect of *Benincasa hispida extract* on fasting serum glucose level in dexamethasone induced diabetic animal model.

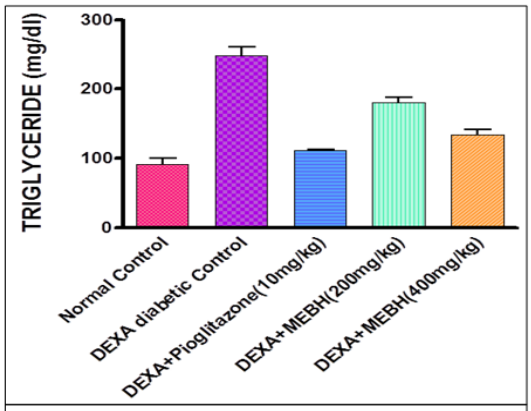

Figure 2: Effect *Benincasa hispida extract* on fasting serum triglyceride level in dexamethasone induced diabetic animal model.

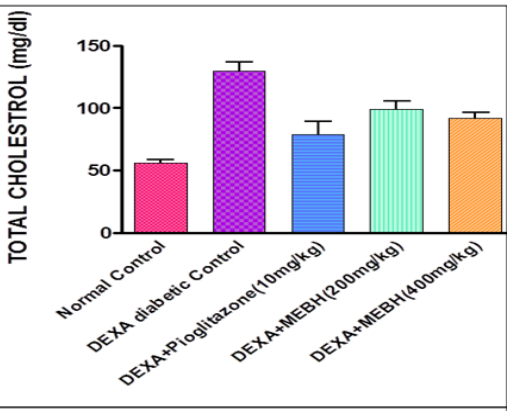

Figure 3: Effect *Benincasa hispida extract* on fasting serum total cholestrol level in dexamethasone induced diabetic animal model.

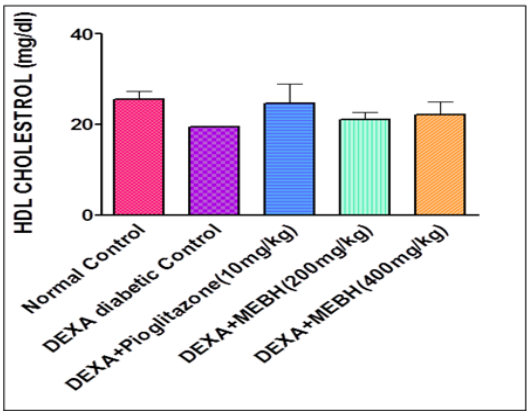

Figure 4: Effect *Benincasa hispida* extract on fasting serum HDL cholestrol level in dexamethasone induced diabetic animal model.

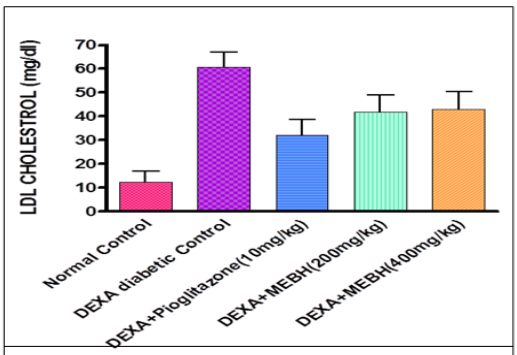

Figure 5: Effect of *Benincasa hispida* extract on fasting serum LDL cholestrol level in dexamethasone induced diabetic animal model.

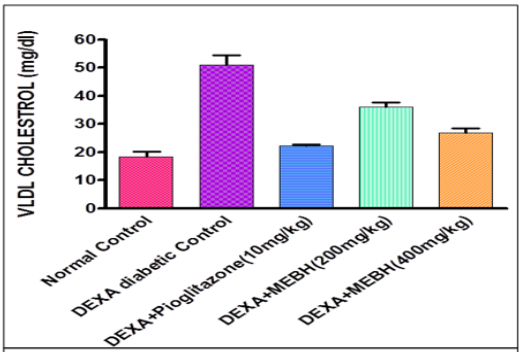

Figure 6: Effect of *Benincasa hispida* on fasting serum VLDL cholestrol level in dexamethasone induced diabetic animal model.

3.2) Body Weight: The results of change in body weight observed during the experimental period for the different groups are as indicated in Table No:1. Administration of dexamethasone 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 pioglitazone, 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 (pioglitazone 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).

3.3) Histopathological Observation Of Liver: Liver parenchyma with intact architecture was seen in standard drug treated rats, low dose & high dose treated rats and non diabetic rats compared to loss of liver parenchyma cells architecture in Group II (untreated diabetic rats). In addition standard drug treated rats, low dose & high dose treated rats showed some hepatocytes with degenerative changes with mild to moderate glycogen content compared to hepatocytes having decreased glycogen content in Group II (untreated diabetic rats), refer fig. 7-18 below.

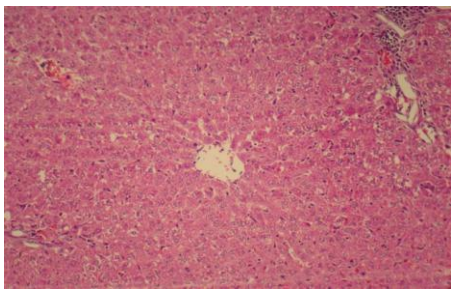

Fig.7 [H&E, x100]

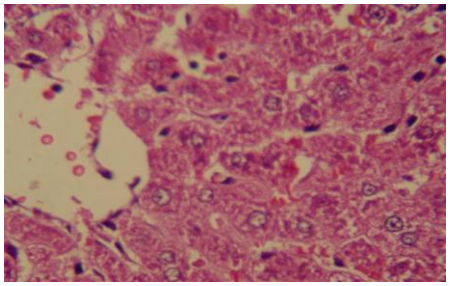

Fig.8 [H&E, x400]

Group I (Non-Diabetic Control Rats): Liver parenchyma with intact architecture. The central vein, portal triad, perivenular and periportal region appers unremarkable. The hepatocytes are arranged in array separated by sinusoids. Shows normal glycogen content within the hepatocytes.

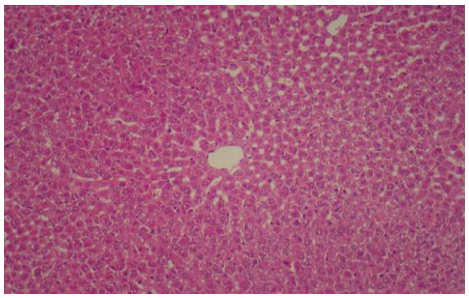

Fig.9 [H&E, x100]

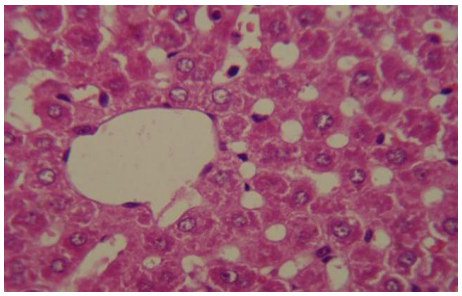

Fig.10 [H&E, x400]

Group II (Untreated Diabetic Rats): Liver parenchyma with loss of architecture. Most of the hepatocytes [>50%] show intracytoplasmic vacuoles and degenerative changes while few show apoptosis. Shows decreased glycogen content within the hepatocytes. The large and small intracytoplasmic vacuoles remain unstained.

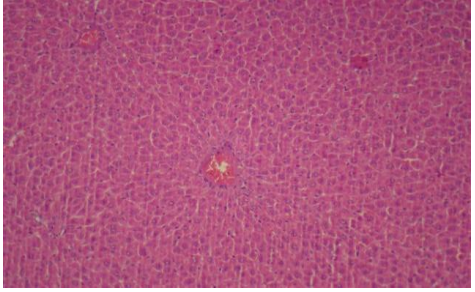

Fig.11 [H&E, x100]

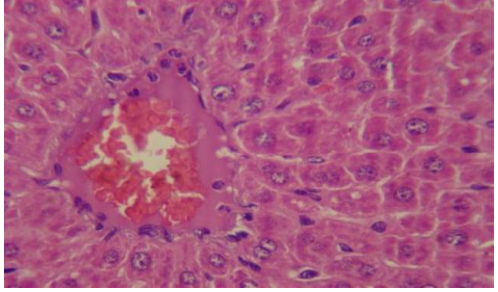

Fig.12 [H&E, x400]

Group III (Pioglitazone Treated Diabetic Rats): Liver parenchyma with intact architecture. The periportal regions appear unremarkable. Shows moderate glycogen content [>60%] within the hepatocytes.

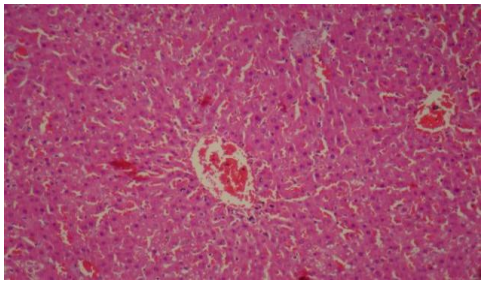

Fig.13 [H&E, x100]

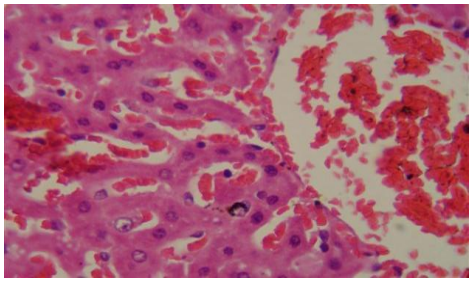

Fig.14 [H&E, x400]

Group IV (Low Dose Extract Treated Diabetic Rats): Liver parenchyma with intact architecture . Some of the hepatocytes show degenerative changes. [The degenerative hepatocytes are less compared to the dexamethasone control group]. The sinusoids appear disrupted. Shows mild glycogen content [>30%] within the hepatocytes.

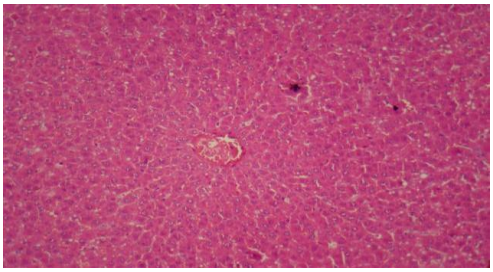

Fig. 15 [H&E, x100]

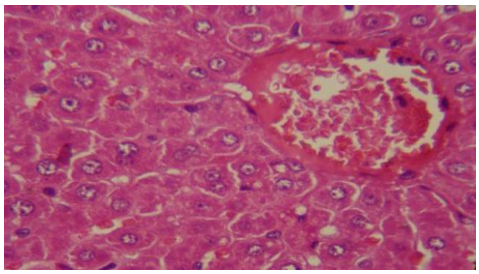

Fig.16 [H&E, x400]

Group V (High dose extract treated diabetic rats): Liver parenchyma with intact architecture. Some of the hepatocytes show degenerative changes. [The degenerative hepatocytes are less compared to the dexamethasone control group]. The sinusoids appear unremarkable. Section studied shows moderate glycogen content [>50%] within the hepatocytes.

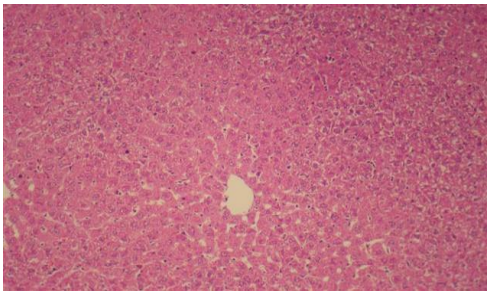

Fig.17 [H&E, x100]

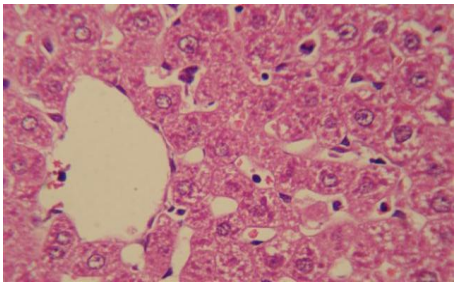

Fig.18 [H&E, x400]

Group VI (High dose extract treated non-diabetic rats): Liver parenchyma with intact architecture. The central vein, portal triad, perivenular and periportal region appers unremarkable. The hepatocytes are arranged in array separated by sinusoids. Shows normal glycogen content within the hepatocytes.

IV. Discussion

Glycaemia and diabetes are rising globally, driven both by population growth, ageing people and by increasing age-specific prevalence. Effective preventive interventions are needed, and health systems should prepare to detect and manage diabetes and its sequelae[12]. Though there have been a flood of molecules and research for new ones for treatment of diabetes, still the problem continues to rise in the world. It is a huge drain on the economy of developing countries, especially with a country like India with a population of above billion people. 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 dexamethasone 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[9]. A study by Jayasree et al at dosage of 200 and 400 mg/kg body weight showed significant hypoglycemic activity in male wistar rats[13]. 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[10].

In this study both low and high dose of extract showed significant ($p<0.05$) decrease in serum triglyceride, total cholesterol and VLDL level when compared with untreated dexamethasone 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 pioglitazone treated groups, the reason for which could not be ascertained. Previous studies have shown that the inhibition of peroxisome proliferator activated receptors(PPAR□) could reduce fat and body weight and improve insulin resistance via the modulation of genes related to lipid and glucose metabolism[14,15,16] Many herbal or natural medicines, that act as modulators of PPARs, have been reported to block intracellular lipid accumulation and lipogenesis and to improve insulin resistance[17,18]. 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. Its pharmacological mechanism may result from the suppression of Peroxisome proliferator-activated receptors (PPAR) signaling and HMG-CoA reductase[19].

Administration of pioglitazone, 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 pioglitazone and high dose extract treated diabetic rats ($p<0.05$) whereas it was not significant for Group IV (low dose extract treated diabetic rats). A study by Sheela K et al relived a slight increase in body weight and protein in streptozotocin induced diabetic rats[20]. In the current study both low dose and high dose extract rats (Group IV & V) revealed liver parenchyma with intact architecture with mild glycogen content in hepatocytes compared to pioglitazone treated diabetic rats. Thus establishing the restorative or hepatoprotectivity activity of Benincasa Hispida extract in diabetic rats.

The above finding indicate that the methanolic extract of Benincasa hispida can be effectively used in insulin resistance conditions. Our studies suggest that methanolic extract of Benincasa hispida is effective in bringing back glycemic and lipemic levels to normal in dexamethasone induced hyperglycemia, hypercholesterolemia and hypertriglyceridemia in albino rats. The probable mechanism involved might be improved insulin sensitivity or restore insulin sensitivity in various organs especially the muscle and the liver in a manner similar to thiazolidinedione derivative (pioglitazone). Further studies into these aspects might reveal the actual mechanisms involved in anti-diabetic activity of methanolic extract of Benincasa hispida.

V. Conclusion

Our study clearly establishes the hypoglycemic effect of Benincasa hispida extract in dexamethasone induced diabetic rat models. 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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