International Journal of Research and Development in Pharmacy and Life Sciences
Available online at http//www.ijrdpl.com
April - May, 2014, Vol. 3, No.3, pp 1004-1010
ISSN: 2278-0238

Research Article

EVALUATION OF ANTIDIABETIC, ANTIDYSLIPIDEMIC & HEPATOPROTECTIVE ACTIVITY OF *HOMALIUM ZEYLANICUM* IN ALLOXAN INDUCED DIABETIC RATS

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(Received: January 30, 2014; **Accepted:** March 22, 2014**)**

ABSTRACT

To evaluate the antidiabetic activity of Homalium zeylanicum stem bark extracts against Alloxan induced Diabetes mellitus. **Materials and methods:** Diabetes was induced in male Wistar rats by intraperitoneal injection of Alloxan (90mg/kg). Ethanol extract of Homalium zeylanicum stem bark were administered to the experimental rats (250mg and 500mg/kg, p.o. for 28 days). The antidiabetic & antidyslipidemic, effects of these extracts was evaluated by the assay of biochemical parameters (Blood glucose and lipid profiles, SGOT, SGPT) and histopathological studies of the liver. **Results:** In Ethanol extract-treated animals, the hyperglycemia by the Alloxan was controlled significantly by restoration of the levels of serum glucose, lipid profile and liver enzymes as compared to the normal and the standard drug Metformin treated groups. Histology of the liver sections of the animals treated with the extracts showed the presence of normal hepatics, absence of necrosis and fatty infiltration, which further evidenced the hepatoprotective activity. **Conclusion:** Ethanol extract of the stem bark of Homalium zeylanicum possesses significant antidiabetic, antidyslipidemic and hepatoprotective activity.

Keywords: Antidiabetic, antidyslipidemic, hepatoprotective, Homalium zeylanicum, Alloxan monohydrate.

INTRODUCTION

Diabetes mellitus or simply diabetes is a chronic, multisystem heterogeneous metabolic disorder that requires lifelong care and at present remains without cure (ADA, 2010). It is a metabolic disorder of multiple etiologies, characterized by chronic hyperglycemia (high circulating glucose) together with disturbances of carbohydrate, fat and protein metabolism resulting from defects of insulin secretion, insulin action or both (ADA, 2008; Gavin et al., 2003) The relative contribution of these disturbances varies between different types of diabetes. The hyperglycemia attacks both microvessels and macrovessels throughout the body resulting in the development of the specific microvascular complications of retinopathy, which can lead to blindness, nephropathy with potential renal failure, and neuropathy. The latter carries the risk of foot ulcers and amputation and also autonomic nerve dysfunction. Diabetes is also associated with an increased risk of macrovascular disease (Feldman, 2003). Diabetes has reached epidemic proportion and has become one of the most challenging health problems of the 21st century. The number of people with diabetes in the year 2010 is estimated to be 285 million, representing 7% of the adult world population and by the year 2030, an estimated 439 million individuals worldwide will have this disorder with the most marked increase projected for the population greater than 65 years of age (Unwin, 2010).

The third group consists of other less common types of diabetes that are caused or associated with certain specific conditions and/or syndromes. The last group includes diabetes diagnosed during pregnancy, called Gestational

Diabetes Mellitus' (GDM) (ADA, 2008). Besides, there is an intermediate group of individuals whose glucose level, although not meeting criteria for diabetes are nevertheless too high to be considered normal. This group consists of individuals that have 'Impaired Fasting Glucose (IFG) and/or Impaired Glucose Tolerance (IGT) and is referred to as "pre-diabetes" as progression to overt diabetes is common, particularly when therapeutic interventions such as lifestyle changes or medications are not provided. (Gavin et al., 2003; Diabetes Prevention Program Research Group, 2002; DREAM, 2006).

The type 1 diabetes mellitus (previously referred to as insulin-dependent diabetes mellitus (IDDM) or juvenile onset diabetes) results from a progressive cellular mediated autoimmune destruction of the pancreatic β-cells that leads to complete insulin deficiency (Knip & Siljander, 2008).

The patients with type 1 diabetes are severely insulin deficient and are dependent on insulin treatment for their survival. At the latter stage of this disease, there is little or no insulin secretion, as manifested by low or undetectable levels of plasma C-peptide (Knip & Siljander 2008). Markers of the immune β-cell destruction include islet cell autoantibodies (ICAs), e.g., autoantibodies to islet cell antigen 512 (ICA512), insulin autoantibodies (IAAs),glutamic acid decarboxylase autoantibodies (GAD65) and autoantibodies to the tyrosine phosphatases, IA-2 and IA-2α. At least one or more of these autoantibodies are present in approximately 85- 90% of the new-onset patients, and therefore can be used clinically to help make the diagnosis (Taplin & Barker 2008). Type 2 diabetes is characterized by complex metabolic derangements, with two main metabolic defects: insulin resistance, a decreased response of peripheral tissues to insulin and β-cell dysfunction that is manifested as inadequate insulin secretion or relative insulin deficiency in the face of insulin resistance and hyperglycemia (DeFronzo, 2004).

The capacity of insulin secretion in these patients is often enough to prevent ketosis and ketoacidosis, but still manifest during periods of severe stress or acute medical illness. So at least initially, and often throughout their lifetime, these individuals do not need insulin treatment to survive (Muoio & Newgard, 2008). The risk for diabetes increases as the body mass index (a measure of body fat content) increases. It is not only the absolute amount but also the distribution of body fat that has an effect on insulin sensitivity: visceral obesity (abdominal fat) is more likely to be linked with insulin resistance hence with type 2 diabetes than is peripheral obesity (gluteal/subcutaneous fat depots) (Kahn et al., 2006).

The recent large-scale genomewide association studies have identified over a dozen susceptibility loci. However, the genetics of this form of diabetes is complex and not clearly defined (Frayling, 2007; Zeggini et al., 2008). These forms of diabetes are frequently characterized by onset of hyperglycemia at an early age, usually before age 25 and sometimes even in the neonatal period and are referred to as Maturity Onset Diabetes of the Young (MODY) (Fajans et al., 2001).

A second form but first to be implicated in MODY is associated with mutations in the glucokinase gene on chromosome 7p and results in a defective glucokinase molecule (Njolstad et al., 2003). The microcirculation also has regulatory systems such as vasomotion, permeability, and myogenic responses that can adapt flow to local metabolic needs (Sheetz & King, 2002). However, much of the impact of chronic diabetes falls on the microcirculation (Skyler, 1996). In fact, the disturbances in microvascular function may arise before overt hyperglycemia and vascular pathologic changes (Sheetz & King, 2002).

MATERIALS AND METHODS

Collection of plant material and preparation of extract:

Plant material used in this study consisted of bark of Homalium zeylanicum(HZ), collected in and around Tirumala hills, Andhra pradesh. The plant was authenticated by Dr. Madhava chetti, Dept. Of Botany, S.V University, Tirupathi.

Plant profile:

Homalium zeylanicum(HZ) Subcanopy trees in wet evergreen forests up to 900 m, and its Bark smooth, grey; blaze white with orange speckles, Branchlets slender, terete, glabrous, Leaves simple, alternate, distichous; stipules caducous; petiole 0.5-1.3 cm long, glabrous; planoconvex in cross section; lamina 7.5-13 x 3.6- 7.6 cm, elliptic, apex abruptly acuminate, base acute or rounded to subattenuate, margin crenate, chartaceous, glabrous; midrib flat above; secondary nerves 6-8 pairs, gradually curved; tertiary nerves reticulo-percurrent, Inflorescence long, slender spikes with interrupted

clusters of small flowers; flowers generally greenish white, sometimes few clusters crimson red in the same spike, FRUIT Capsule; seeds small, many, oblong or angular.

Chemicals: Ethanol, glacial acetic acid general reagents etc.

Preparation of plant extract:

The stem bark were dried in shade and ground to fine powder. This powder (150-180g) was extracted with soxhlet apparatus for 48 hours using 1.5 liters of ethanol .The alcholic extract was filtered with filter paper, filtrate was collected and evaporated under reduced pressure using vacuum evaporator. The concentrated material obtained was reduced to thick mass at room temperature and water was removed by placing it in dessicator. The extract was dissolved in water and used for the studies.

Animals: Healthy, adult male albino wistar rats between 2 and 3 months of age and weighing between 150-200g were used for the study. The animals were procured from Sainath agencies, Hyderabad. The animals were kept in polypropylene cages (6 in each cage) and animals were acclimatized to our lab environment for about a week prior to the study, so that they could adapt to the new environment. Animal house were maintained under standard hygienic conditions, at 25 ± 20C, humidity (60 ± 10 %) with 12 hrs day and night cycle, with food and water ad libitum. The experiments were carried out prior approval from Institutional Animal Ethical Committee (IAEC).

Experimental design:

All animals were divided in to 5 groups each consists (n=6)

Group I: Normal given Sod.CMC (p.o)

Group II : Diabetic control (Alloxan 120mg/kg, i.p)

Group III: Diabetic+ Root extract (250mg/kg, p.o)

Group IV: Diabetic+ Root extract (500mg/kg, p.o)

Group V: Diabetic+ Metformin (10mg/kg)

Biochemical evaluation

Blood samples were drawn from the retro orbital puncture in different time points in oral glucose test (OGT), and on 1st 7th 14th 21st 28th day estimated blood glucose levels and estimated Lipid profiles and SGOT, SGPT levels end of the study that is 28th day and all the samples were centrifuged at 1000 g for 10 min, In order to determine the blood glucose levels(Trinder, 1969) , OGT test, lipid profiles (Bucolo, 1973) and SGOT & SGPT activity(Reitman et al., 1957).

Statistical analysis

The data are presented as mean ± S.D Statistical comparisons were made by one-way analysis of variance (ANOVA) and followed by Student-Neuman-Keuls as the post hoc test. Data were considered significant when p values were lower than 0.05.

RESULTS

The mean blood glucose level values in normal (negative control), diabetic untreated (positive control) and diabetic rats treated with ethanolic extract of Homalium zeylanicum and diabetic control group rats were compared with treated group rats. The blood glucose level values were significantly raised in alloxan induced diabetic groups. Where as in the treatment groups treated with H.Z and Metformin the blood glucose levels were found to be decreased compared to inducing group. The blood glucose level values in normal (negative control), diabetic untreated (positive control) and diabetic rats treated with ethanolic extract of Homalium zeylanicum is presented in fig 1. Diabetic control group rats were compared with treated group rats.

The oral glucose tolerance (OGT) values were significantly raised at 30min, where as in the treatment groups treated with H.Z and Metformin the blood glucose levels were gradually decreased at 60mins, 90mins & 120mins compared to inducing group fig 2.

The mean body weight values in normal (negative control), diabetic untreated (positive control) and diabetic rats treated with ethanolic extract of Homalium zeylanicum is presented in Table 1. Diabetic control group rats were compared with treated group rats.

The body weight values were significantly decreased in alloxan induced diabetic groups. Where as in the treatment groups treated with H.Z and Metformin the body weight were found to be increased compared to inducing group.

The mean SGOT & SGPT level values in normal (negative control), diabetic untreated (positive control) and diabetic rats treated with ethanolic extract of Homalium zeylanicum is presented in Table 2. Diabetic control group rats were compared with treated group rats.

The SGOT & SGPT level values were significantly raised in alloxan induced diabetic groups. Where as in the treatment groups treated with H.Z and Metformin the SGOT & SGPT

levels were found to be reduced compared to inducing group.

The mean TC, HDL & TG levels in normal (negative control), diabetic untreated (positive control) and diabetic rats treated with ethanolic extract of Homalium zeylanicum is presented in Table 3. Diabetic control group rats were compared with treated group rats.

The TC, HDL & TG levels were significantly raised in alloxan induced diabetic groups. Where as in the treatment groups treated with H.Z and Metformin the TC, TG levels were found to be decreased but increased HDL levels compared to inducing group.

Histopathological reports shows that in different groups as follows A) Normal rats show normal islets. B) Alloxan (120 mg/ kg) induced diabetic rats shows abnormal.C) H, Z 250 mg/kg treated rats. The structure of pancreas is partially effaced. D) H, Z.500mg/kg treated rats. The islets are normal. E) Metformine (10mg/kg) treated rats the islets are normal which is represented in fig 3.

DISCUSSION

Management of diabetes with the agents devoid of any side effects is still a challenge to the medical system. This concern has led to an increased demand for natural products with antihyperglycaemic activity, having fewer side effects. Alloxan causes diabetes through its ability to destroy the insulin-producing beta cells of the pancreas (Lenzen S, Panten U, 1988). In vitro studies have shown that alloxan is selectively toxic to pancreatic beta cells, leading to the induction of cell necrosis. The cytotoxic action of alloxan is mediated by reactive oxygen species, with a simultaneous massive increase in cytosolic calcium concentration, leading to a rapid destruction of beta cells (Szkudelski T, 2001).

According to earlier studies, plant extracts because antihyperglycemic effect by promoting regener-ation of β-cells or by protecting these cells from destruction, by restricting glucose load as well as by promoting unrestricted endogenous insulin action. Antihyperglycemic effect may also be caused by the effect of plant extract contains flavonoids shows effect on β-cells to release insulin or activate the insulin receptors to reduce the blood sugar and stimulate the peripheral glucose consumption (McLennan et al., 1991). That flavonoids protects against oxidative stress-induced cellular damage as well as chelatory property(Mira et al., 2002; Anjaneyulu et al., 2004; Furusawa et al., 2005). Anti-diabetic potency of flavonoids, particularly hesperidin and quercetin, has been highlighted in many reports and attributed in part to their antioxidant and hypoglycemic effects(Frode and Medeiros 2008; Lean et al., 1999; Jung et al., 2006).

Flavonoids inhibited the dyslipidemia in our study reported that flavones can inhibit lipogenesis and lower plasmatic triglycerides levels by enhancing LDL receptors expression and increasing fat bile rejection. 26 From the results of clinical studies Insulin resistance was compensated by the enhanced insulin secretion, whereas persistently elevated free fatty acids may contribute to progressive β-cell failure (β-cell lipotoxicity) in individuals genetically predisposed to DM2(Knekt et al., 2002; Santomauro et al., 1999). A possible mechanism of the Homalium zeylanicum extract as Hepatoprotective may be due to its anti-oxidant effect or inhibition of Cytochrome P450. This might be due to the higher contents of flavonoids present in the extract which could have reduced hyperglycemia, dyslipidemia, and elevated liver enzymes

The present experimental studies reveal that the ethanolic and extract from Homalium zeylanicum bark (250 mg/kg & 500mg/kg) administered orally for 28 days produced a significant decrease in the blood glucose level in the model of alloxan-induced diabetes and glucose tolerance test in rats. The comparable effect of the plant extract with metformin may suggest similar mode of action. As compared to ethanolic extract exhibits anti-diabetic activity. The histopathological changes in the pancreas support the biochemical changes which showed some histological changes. The present investigation hence proves the traditional claim regarding Homalium zeylanicum for its anti-diabetic activity.

CONCLUSION

In the present investigation, oral administration of H.Z to glucose overloaded rats exhibited improved oral glucose tolerance, normoglycemic rats showed hypoglycaemic effect, and on 28days continuous treatment in alloxan-induced diabetic rats demonstrated prominent reduction and normalization of elevated blood sugar levels i.e. antihyperglycemic or antidiabetic effect, comparing to respective control rats. Therefore, it can be concluded that

the ethanol extract of Homalium zeylanicum bark possessed remarkably effective antidiabetic and antidyslipidemic, Hepatoprotective potential against alloxan-induced diabetes rats substantiating its traditional usage in India.

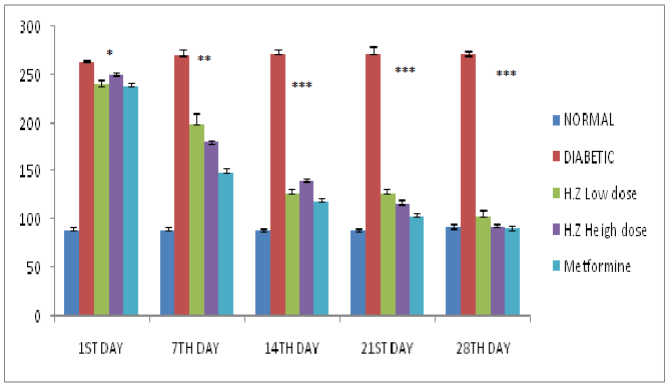


Fig1. Blood glucose level (mg/dl) in normal control, Dibetic control and treated Homalium Zeylanicum groups. (Data was expressed Mean±SD (n=6) values were significant when *p<0.05, **p<0.01, ***p<0.001, compared between diabetic control and treated groups.)

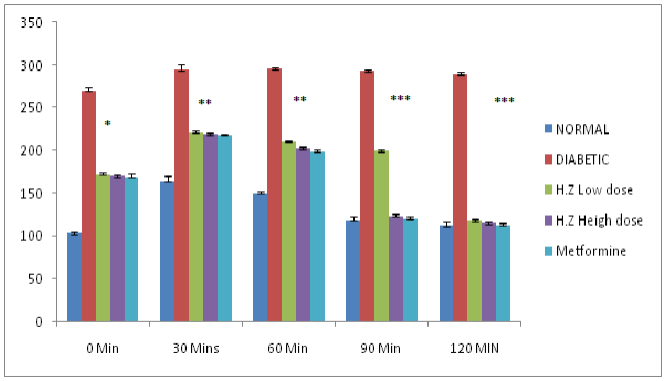
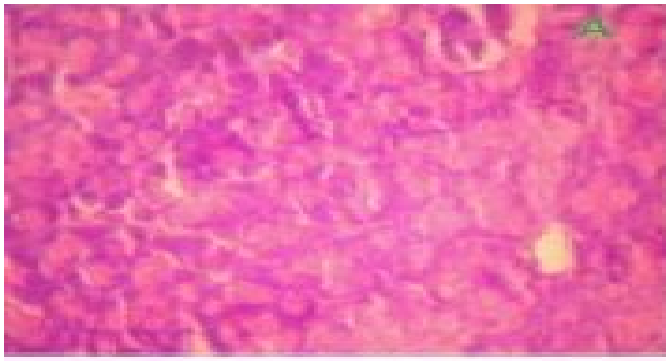


Fig2. Blood glucose level (mg/dl) in normal control, Diabetic control and treated Homalium Zeylanicum groups(Data was expressed Mean±SD (n=6) values were significant when *p<0.05, **p<0.01, ***p<0.001, compared between diabetic control and treated groups).



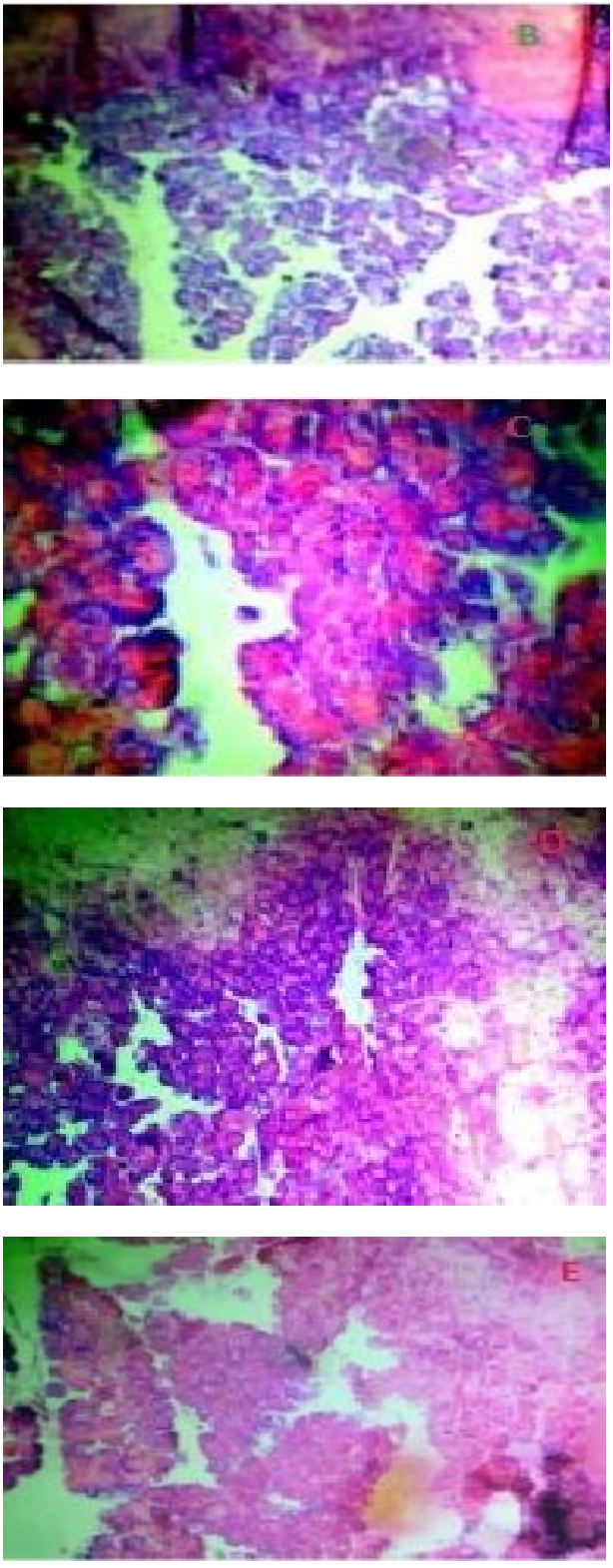


Fig 3: Histopathological reports shows that in different groups as follows **A)** Normal rats show normal islets. **B)** Alloxan (120 mg/ kg) induced diabetic rats shows abnormal. **C)** H, Z 250 mg/kg treated rats. The structure of pancreas is partially effaced. **D)** H, Z.500mg/kg treated rats. The islets are normal. **E)** Metformine (10mg/kg) treated rats the islets are normal.

Table 1. Body weight (grams) in Normal control, diabetic control and Homalium Zeylanicum Treated Groups

GROUP	1st day MEAN ± SD	7th day MEAN ± SD	14th day MEAN ± SD	21st day MEAN ± SD	28th day MEAN ± SD
Normal control	220 ± 2.09	222 ± 2.75	221 ± 3.46	225 ± 1.78	228 ± 1.78
Diabetic control	230 ± 2	170 ± 3.89	153 ± 7.04	145 ± 3.16	131 ± 3.03
H.Z (250mg/kg)	221.5 ± 3.08 **	164.16 ± 5.3 *	165 ± 1.78 **	170 ± 2.09 **	174 ± 2.28 **
H.Z (500mg/kg)	225 ± 2.09 **	168 ± 3.34 ns	175 ± 1.78 **	180± 2.75 **	186 ± 2.82 **
Metformine(10mg/kg)	220 ± 1.78 **	170 ± 3.57 ns	180 ± 3.16 **	185 ± 1.41 **	190 ± 2.6 *

All treatment groups were compared with Diabetic control group, data was expressed Mean±SD (n=6). The significance between two groups was determined by one way ANOVA , followed by Dunnett multiple comparision, *p<0.05, **p<0.01, ***p<0.001

Table 2. SGOT, SGPT Levels in Normal control, diabetic control and Homalium Zeylanicum Treated Groups

Groups	SGOT(IU) MEAN ± SD	SGPT(IU) MEAN ± SD
Normal control	96 ± 2.6	86 ± 3.68
Diabetic control	120.2 ± 2.89	116 ± 2.82
H.Z (250mg/kg)	112.3 ± 1.28 **	105.66 ± 3.38 **
H.Z (500mg/kg)	107 ± 3.57 **	102 ± 3.4 **
Metformine(10mg/kg)	98 ± 3.16 **	90 ± 6.35 **

The data was expressed Mean±SD (n=6). The significance between two groups was determined by one way ANOVA , followed by Dunnett multiple comparision, *p<0.05, **p<0.01, ***p<0.001.

Table 3: TC, TG, HDL Levels in Normal control, diabetic control and Homalium Zeylanicum Treated Groups.

GROUPS	Total cholesterol (mg/dl) MEAN ± SD	Triglycerides (mg/dl) MEAN ± SD	HDL(mg/dl) MEAN ± SD
Normal	98.5 ± 2.79	85.3 ± 2.06	42.66 ± 2.16
Diabetic control	215.3 ± 3.77	145 ± 3.89	20.3 ± 1.63
H.Z (250mg/kg)	135.3 ± 3.31 *	102.08 ± 3.16 *	39.49 ± 1.85 *
H.Z (500mg/kg)	122.66 ± 3.77 **	96.3 ± 1.86 **	40 ± 1.41 **
Metformine(10mg/kg)	105.8 ± 3.37 **	92.25 ± 1.08 **	42.83 ± 1.94 **

Data was expressed Mean±SD (n=6) values were significant when *p<0.05, **p<0.01, ***p<0.001, compared between diabetic control and treated groups.

Acknowledgement:

First author is thankful to Dr. B. Agaiah Goud, Principal& Chairman, SRR College of Pharmaceutical Sciences, for the providing necessary facilities for completion of the work.

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How to cite your article:

Pothireddy S., Chukka S., Shankaraiah P., "Evaluation of antidiabetic, antidyslipidemic & hepatoprotective activity of Homalium zeylanicum in alloxan induced diabetic rats", Int. J. Res. Dev. Pharm. L. Sci., 2014, 3(3), pp. 1004-1010.

