

## Evaluation of Antidiabetic, Antihyperlipidemic and Antioxidant Activities of *Acacia leucophloea* in Streptozotocin-Nicotinamide Induced Type II Diabetic in Rats

<sup>1</sup>M. Madhavi, <sup>2</sup>S. Kiran and <sup>2</sup>D. Ramesh

<sup>1</sup>Department of Pharmacology, Vaagdevi College of Pharmacy,  
<sup>2</sup>Ramnagar, Hanamkonda, Warangal-506001 andhra Pradesh, India

**Abstract:** The present study was investigated for phytochemical screening and anti-diabetic, antihyperlipidemic, antioxidant activities of *Acacia leucophloea* in streptozotocin-nicotinamide induced type II diabetes in rats. In the present study thirty rats were randomly classified into five groups. The first group was served as a control. The second group was served as Diabetic control. The third group was served as Standard (Glibenclamide 10mg/kg), fourth group was served as test 1 administered with 200 mg/kg and fifth group was served as test 2 administered with 400 mg/kg of Ethanolic extracts of *Acacia leucophloea* stem bark in a daily oral dose for 14 days. Type II diabetes was induced in overnight fasted rats by a single intraperitoneal injection of 60mg/kg streptozotocin, 15 min after the i.p. administration of 120mg/kg body weight of nicotinamide. Hyperglycemia was confirmed by the elevated glucose levels in plasma, determined at 72 h and then on day 7 after injection of inducing agents. Treatment of animals with extracts of *Acacia leucophloea* in a daily dose of 200 and 400 mg/kg for 14 consecutive days significantly mitigated the induced changes in the glucose, lipid profile, oxidative stress, liver enzymes and body weight parameters. The induced alterations in the oxidant and antioxidant parameters were also improved. Conclusively, ethanolic extract of *Acacia leucophloea* stem bark treatment exhibited marked beneficial effects against streptozotocin-nicotinamide induced diabetes.

**Key words:** Diabetes • *Acacia Leucophloea* • Hyperlipidemia • Oxidative Stress

### INTRODUCTION

Diabetes is a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both. The chronic hyperglycemia of diabetes is associated with long-term damage, dysfunction and failure of different organs, especially the eyes, kidneys, nerves, heart and blood vessels [1].

Type II diabetes has emerged as a leading cause of death and disability worldwide [2,3]. The International Diabetes Federation predicts that the number of people living with diabetes will rise from 366 million in 2011 to 552 million by 2030 [4]. The disease is a major degenerative ailment in the world today, affecting at least 15 million people and having complications which include

hypertension, atherosclerosis and microcirculatory disorders [5]. The WHO has recommended the evaluation of traditional plant treatments for management of diabetes as they are effective, less toxic with minimum or no side effects and are considered to be excellent formulations for oral therapy [6].

*Acacia leucophloea* (Mimosoideae), commonly known as “safed babul” is a large thorny tree attaining heights of 35 m and diameters at breast height of 100 cm [7]. Its largest continuous distribution is arid India through Sri Lanka, Bangladesh, Burma and much of Thailand [8]. The chemical constituents found are n-Hexacosanol,  $\beta$ -Amyrin,  $\beta$ -Sitosterol, Tannins [9]. The barks of plant are used in traditional medicine as an astringent, a bitter, a thermogenic, a styptic, a preventive of infections, an anthelmintic, a vulnerary, a demulcent,

**Corresponding Author:** M. Madhavi, Department of Pharmacology, Vaagdevi College of Pharmacy,  
Ramnagar, Hanamkonda, Warangal - 506001 Andhra Pradesh, India.  
Mob: +918885604358.

an expectorant, an antipyretic, an antidote for snake bites and in the treatment of bronchitis, dry cough, vomiting, wounds, ulcers, diabetes, diarrhea, dysentery, internal and external hemorrhages, dental caries stomatitis, intermittent fevers and skin diseases [10- 14]. An extract of stem bark and leaves of the plant is applied twice daily to cure psoriasis [15]. Bark and leaves are used to treat renal edema, cardiac edema and indigestion. Leaf juice is used to treat fever and stomachache and, mixed with cow's milk, to treat bleeding piles [16]. Traditionally all parts of plants are used against cancer, inflammation, ophthalmalgia, leprosy and to treat bleeding piles. Leaves are believed to possess hypotensive, CNS-depressant, antisyphilitic and antimicrobial activities while gums possess demulcent properties [17]. Its gum and decoction of Bark is used for contraception and menstrual complaints [18]. Inner bark inner bark is used to manufacture dyes and tannins [19].

Various extracts of this plant have been reported to possess antioxidant [20], antipyretic [21], antiplatelet [22], wound healing [23], anti-diarrheal [24], anti-inflammatory, antibacterial [25], free radical scavenging activities [26], antimicrobial [27].

## MATERIALS AND METHODS

**Plant Material:** The plant *Acacia leucophloea* was collected from waste lands of Kakatiya University during the month of March 2013 and authenticated by an expert taxonomist Dr. V.S.Raju Department of Botany, Kakatiya University, Warangal andhra Pradesh, India.

**Chemicals:** Glibenclamide was obtained as a gift sample from Suzikem Drugs Pvt. Ltd. Hyderabad. Streptozotocin was purchased from Sigma Aldrich, Germany. Total cholesterol, triglyceride, HDL kits were purchased from CPC diagnostics Pvt. Ltd. Hyderabad. Antioxidant kits were purchased from Himedia Pvt. Ltd. Mumbai, Where as other biochemical kits were obtained from Span Diagnostic Ltd. India.

**Animals:** Healthy Wistar albino male rats weighing 150-200 g were used for the study which was procured from Sanzyme Scientifics, Hyderabad. They were housed individually in polypropylene cages, maintained under standard conditions (12h light and 12h dark cycle, 25±30°C, 35-60% relative humidity), the animals were fed with standard rat pellet diet and water *ad libitum*. The experiments planned after the approval of Institutional Animal Ethical Committee (IAEC), Vaagdevi College of Pharmacy, Warangal andhra Pradesh.

**Preparation of Plant Extract:** Freshly collected stem barks of *Acacia leucophloea* were dried in shade and pulverized to a coarse powder and extracted with ethanol using the Soxhlet apparatus. The filtrate obtained was evaporated to dryness at 50-65°C in a rotary vacuum evaporator to obtain a dark coloured molten mass [13].

**Qualitative Phytochemical Analysis:** Ethanolic extracts of *Acacia leucophloea* stem bark extracts were analyzed for the tannins, sterols, lipids, glycosides, terpenoids, phenols, carbohydrates, anthraquinones, resins, reducing sugar, saponins, flavanoids and alkaloids [42].

**Acute Toxicity Studies:** Acute oral toxicity study was performed as per Organization for Economic Cooperation and Development (OECD) guidelines 423 [28]. Administration of stepwise dose of EEAL (50 mg/kg-2000 mg/kg b.w), animals were observed individually at least once during the first 30 minutes and periodically during the first 24 hours, with special attention given during the first 4 hours and daily thereafter, for total of 14 days. The dose 2000 mg/kg was found to be safe and no toxicity was observed. One-fifth and one-tenth of upper limit dose were selected as the label for examination of antidiabetic activity.

**Oral Glucose Tolerance Test (OGTT):** The oral glucose tolerance test was performed in overnight fasted normal rats. Twenty four rats were divided into four groups (n = 6), group-I was administered with 0.1% sodium carboxy methyl cellulose at a dose of 2ml/kg, group-II was administered with glibenclamide at a dose of 10 mg/kg, groups III and IV were administered with ethanolic extract of *Acacia leucophloea* (EEAL) at a dose of 200 mg/kg and 400 mg/kg respectively. Glucose (3g/kg) was fed 30 min after the administration of extracts. Blood (0.3 ml) was withdrawn from retro-orbital plexus under mild ether anesthesia at a time periods of 0, 30, 60 and 120 min after glucose loading. Plasma was separated from the collected blood samples after centrifugation at 4000 rpm for 15 min. Blood glucose level in plasma was measured using glucose oxidase and peroxidase method [29].

**Hypoglycemic Activity:** Test was performed in overnight fasted normal rats. Twenty four rats were divided into four groups (n=6), group-I was administered with 0.1% sodium carboxy methyl cellulose at a dose of 2 ml/kg, group-II was administered with glibenclamide at a dose of 10 mg/kg, groups III and IV were administered with ethanolic extract of *Acacia leucophloea* (EEAL) at a dose of 200 mg/kg and 400 mg/kg respectively. Blood (0.3 ml) was

withdrawn from retro-orbital plexus under mild ether anesthesia at a time periods of 0, 2, 4 and 6 hours after drug administration [30,31].

**Induction of Type II Diabetes Mellitus:** The animal model of type II diabetes mellitus (NIDDM) was induced in overnight fasted rats by a single intraperitoneal injection of 60 mg/kg STZ, 15 min after the i.p. administration of 120 mg/kg nicotinamide. Hyperglycemia was confirmed by the elevated blood glucose levels in plasma, determined at 72 h after administration. Animals with blood glucose levels more than 126mg/day were used for study. Only rats confirmed with permanent NIDDM were used in the antidiabetic study [32, 43].

**Assessment of Antidiabetic Activity in Streptozotocin-nicotinamide Diabetic Rats:** Male Wistar albino rats were divided into five groups of six rats in each group (n=6) as follows. Group I - Rats served as normal control received 1% CMC daily for 14 days, Group II - Rats served as diabetic control received 1% CMC daily for 14 days, Group III - Diabetic rats received glibenclamide (10 mg/kg) daily for 14 days. Group IV - Diabetic rats received EEAL (200 mg/kg) daily for 14 days, Group V - Diabetic rats received EEAL (400 mg/kg) daily for 14 days. The fasting blood glucose levels were determined on 1, 7 and 14 days using GOD-POD method [33, 43].

**Biochemical Analysis:** The lipid profile includes Total Cholesterol (TC), Triglycerides (TG), High Density Lipoprotein (HDL) were determined by using enzymatic kits [34]. Low Density Lipoproteins (LDL) and Very Low Density Lipoprotein (VLDL) values were calculated by Friedewalds equation [35] as shown below,

$$\text{VLDL} = \text{TG}/5$$

$$\text{LDL} = \text{TC} - (\text{HDL} + \text{VLDL})$$

Serum Glutamate Oxaloacetate Transaminase (SGOT), Serum Glutamate Pyruvate Transaminase (SGPT) estimated by modified IFCC method [36]. Malondialdehyde, catalase and GSH levels were determined according to the selected methods [37, 38].

**Histopathological Studies:** After the end of the study all the rats were sacrificed by cervical dislocation under mild ether anesthesia and pancreas were isolated, washed with cold saline and preserved in 10% formalin solution in

buffered form. Blocks from tissues were routinely processed and embedded in paraffin. Thin sections were cut by using rotary microtome and stained with hematoxylin and eosin for histomorphology evaluation.

## RESULTS

**Phytochemical Screening:** Phytochemical investigation of ethanolic extract of *Acacia leucophloea* stem bark revealed the presence of steroids, alkaloids, carbohydrates, flavonoids, tannins, glycosides, polyphenols, gums and mucilage [45].

**Acute Oral Toxicity Study:** From the acute studies no toxicity was found to dose of 2000mg/kg hence, 1/10<sup>th</sup> (200 mg/kg b.w) and 1/5<sup>th</sup> (400 mg/kg b.w) of this dose was selected for further study.

**Hypoglycemic Effect of Ethanolic Extract of *Acacia Leucophloea*:** The results from the study clearly indicated that the ethanolic extract 200 and 400 mg/kg exhibited significant hypoglycemic activity at 4<sup>th</sup> and 6<sup>th</sup> hours in fasted normal rats. The hypoglycemic activity of EEAL was found to be dose dependent. Standard drug glibenclamide indicated a significant decrease of blood glucose levels (Table 1).

**Effect on Oral Glucose Tolerance Test:** The effects of ethanolic extract of *Acacia leucophloea* (200 mg/kg and 400 mg/kg) on glucose tolerance are shown in (Table 2). By administration of glucose (3 g/kg) produced significant change in blood glucose level of normal rats. The treatment groups with EEAL 200 mg/kg, 400 mg/kg and glibenclamide 10 mg/kg showed significant reduction in plasma glucose level at 60, 120 minutes when compared to normal control group.

**Effect of EEAL on Streptozotocin-nicotinamide Induced Diabetic Rats:** There was a significant increase in blood glucose level in diabetic rats when compared with normal controls due to injection of STZ-NA. In the study, daily administration of the extract for 14 days led to fall in blood glucose levels. At the end of experiment (14<sup>th</sup> day) blood glucose level was (163.66±11.77) and (145.6±13.61) mg/dl at the doses of 200 and 400 mg/kg of EEAL respectively. The antidiabetic effect of EEAL on the blood glucose levels in diabetic rats is also shown in (Table 3).

Table 1: Hypoglycemic effect of Ethanolic extract of *Acacia leucophloea*

Groups	Blood glucose (mg/dl) (Mean ± SD)			
	0hr	2hrs	4 hrs	6 hrs
Control	82.33±6.65	80.83±6.11	79.16±4.30	81.33±2.94
Glibenclamide(10mg/kg)	80.16±7.44	75.16±5.87	69.16±4.26**	74.50±2.73**
EEAL(200mg/kg)	78.50±7.66	76.33±7.50	73.50±4.59	76.33±2.65*
EEAL (400mg/kg)	79.16±7.41	73.83±8.18	69.50±7.06*	74.66±3.98**

Data represents mean ± S.D. (n=6). \*P<0.05 \*\*P<0.01, Significant compared to control analyzed by one-way ANOVA followed by Dunnett's test.

Table 2: Effect on Oral Glucose Tolerance Test of Ethanolic extract of *Acacia leucophloea*

Groups	Blood glucose (mg/dl) (Mean ± SD)			
	0 min	30 min	60 min	120 min
Control	86.50±8.78	114.33±8.21	103.83±8.79	93.33±7.39
Glibenclamide(10mg/kg)	78.83±6.64	92.83±10.16**	78.16±7.11***	73.16±7.41***
EEAL(200mg/kg)	76.16±7.44	101.83±10.79	91.83±10.00	81.16±5.84*
EEAL(400mg/kg)	72.50±13.80	93.66±12.97**	81.33±12.64**	76.16±7.41**

Data represents mean ± S.D. (n=6). \*P<0.05, \*\* P <0.01, \*\*\* P <0.001, Significant compared to control analyzed by one-way ANOVA followed by Dunnett's test

Table 3: Effect on Streptozotocin-Nicotinamide induced Diabetic Rats

Groups	Blood glucose (mg/dl) (Mean ± SD)		
	1 <sup>st</sup> day	7 <sup>th</sup> day	14 <sup>th</sup> day
Control	74.00±4.24	75.66±3.55	77.16±3.43
Diabetic control	230.66±9.26	239.50±13.04	244.50±7.12
Standard(10mg/kg)	213.16±6.11	159.66±7.91***	114.83±6.17***
EEAL(200mg/kg)	221.16±8.90	195.50±12.40***	163.66±11.77***
EEAL(400mg/kg)	218.16±11.90	172.50±10.72***	145.16±13.61***

Data represents mean ± S.D. (n=6). \* P <0.05, \*\* P <0.01, \*\*\* P <0.001, Significant compared to control analyzed by one-way ANOVA followed by Dunnett's test.

Table 4: Effect of Ethanolic extract of *Acacia leucophloea* on lipid profile

Groups	TG(mg/dL)	TC(mg/dL)	HDL (mg/dL)	LDL (mg/dL)	VLDL(mg/dL)
Control	77.48±4.92	74.00±2.05	25.65±2.65	32.85±3.71	15.49±0.98
Diabetic control	181.45±7.05	176.53±2.28	13.28±1.09	126.84±3.41	36.40±1.36
Standard(10mg/kg)	85.56±6.36***	81.88±1.93***	26.78±2.63***	37.95±4.87***	17.11±1.27***
EEAL(200mg/kg)	109.36±5.61***	104.63±2.21***	20.35±2.79**	62.41±3.87***	21.87±1.12***
EEAL(400mg/kg)	96.98±5.22***	94.45±1.45***	21.65±6.01**	53.40±6.37***	19.39±1.04***

Data represents mean ± S.D. (n=6). \* P <0.05, \*\* P <0.01, \*\*\* P <0.001 Significant compared to control analyzed by one-way ANOVA followed by Dunnett's test.

**Effect of Eeal on Lipid Profile:** In the present study the total cholesterol, triglycerides, LDL and VLDL were reduced in diabetic rats by treating with EEAL for 14 days. HDL level was significantly improved by treatment with EEAL as compared to diabetic control group (Table 4). The results of present study indicated that the ethanolic extract of *Acacia leucophloea* stem bark possesses significant hypolipidemic activity.

**Effect of Eeai on Liver Enzymes:** In diabetic control rats there was gradual increase in SGOT and SGPT parameters, the groups treated with EEAL (200 and 400 mg/kg)

showed a significant reduction in these parameters when compared to diabetic control group, the reduction of these parameters by treated with EEAL at 400 mg/kg was comparable with that of the glibenclamide treated group (Table 5).

**Antioxidant Activity of EEAL:** (Table 6) shows the effect of administration of EEAL on MDA, CAT and GSH in liver tissue of rats. There was significant ( $p < 0.001$ ) elevation in tissue MDA in diabetic control rats as compared to normal rats. Treatment with EEAL for 14 days resulted in significant ( $p < 0.001$ ) decrease in liver tissue MDA, CAT

Table 5: Effect of Ethanolic extract of *Acacia leucophloea* on liver enzymes

Groups	SGOT (IU/L)	SGPT (IU/L)
Control	36.68±5.87	44.80±4.67
Diabetic control	79.86±4.38	88.73±6.20
Standard(10mg/kg)	38.80±7.21***	39.50±7.62***
EEAL(200mg/kg)	64.43±9.11**	74.38±4.38**
EEAL(400mg/kg)	53.56±3.45***	68.90±6.00***

Data represents mean ± S.D. (n=6). \*  $P < 0.05$ , \*\*  $P < 0.01$ , \*\*\*  $P < 0.001$ , Significant compared to control analyzed by one-way ANOVA followed by Dunnett's test.

Table 6: Effect of Ethanolic extract of *Acacia leucophloea* on oxidative stress

Groups	MDA (nmol./mg protein)	CAT(μmol.H <sub>2</sub> O <sub>2</sub> consumed/ min/mg protein)	GSH (nmols/mg of protein)
Control	27.25±4.36	239.55±6.20	45.32±2.45
Diabetic control	55.03±2.18	165.66±8.09	15.38±3.12
Standard	32.07±2.29***	207.33±11.15**	37.15±4.26**
EEAL (200mg/kg)	44.29±2.06**	179.55±12.93*	23.63±2.45*
EEAL (400mg/kg)	38.37±1.81***	197.33±11.15**	31.34±1.19*

Data represents mean ± S.D. (n=6). \*  $P < 0.05$ , \*\*  $P < 0.01$ , \*\*\*  $P < 0.001$ , Significant compared to control analyzed by one-way ANOVA followed by Dunnett's test.

Table 7: Effect of Ethanolic extract of *Acacia leucophloea* on body weight

Groups	Initial weight	Final weight
Control	188.66±11.36	212.83±13.31
Diabetic control	179.33±12.75	164.50±11.00
Standard(10mg/kg)	197.16±8.88	224.50±9.22***
EEAL(200mg/kg)	174.00±11.13	183.66±13.18*
EEAL(400mg/kg)	178.83±13.13	195.83±9.62***

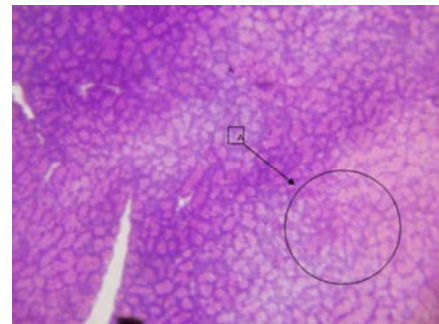
Data represents mean ± S.D. (n=6). \*  $P < 0.05$ , \*\*  $P < 0.01$ , \*\*\*  $P < 0.001$ , Significant compared to control analyzed by one-way ANOVA followed by Dunnett's test.

and GSH contents in diabetic control rats were significantly ( $p < 0.001$ ) depleted in liver tissue when compared with normal rats. EEAL treatment at both dose levels significantly ( $p < 0.001$ ) restored MDA, CAT and GSH levels as compared with diabetic control.

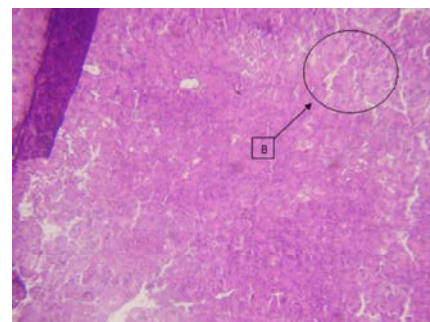
**Effect of Eeai on Body Weight:** The body weight of the diabetic controls (group II) significantly decreased compared with the normal controls (group I). During the observation of the EEAL treated diabetic rats at doses of 200 mg/kg and 400 mg/kg, there were significant ( $p < 0.05$ ) weight gains on day 14 relative to day 0 as shown in (Table 7).

**Histopathological Studies of Pancreas:** Histopathological examination of pancreas showed the destruction of β-cells in the diabetic control group and by treating with EEAL (200 and 400 mg/kg) and glibenclamide (10 mg/kg) showed recovery of damaged tissues when section of treated groups compared with diabetic control (Figure 1).

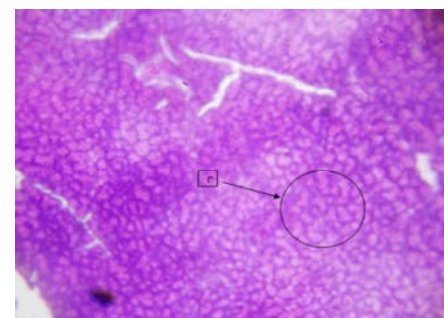
**Histopathology:** The histopathological changes in control, Diabetic control and Ethanolic extract of *Acacia leucophloea* treated groups is shown in Fig. 1.1 to 1.5.



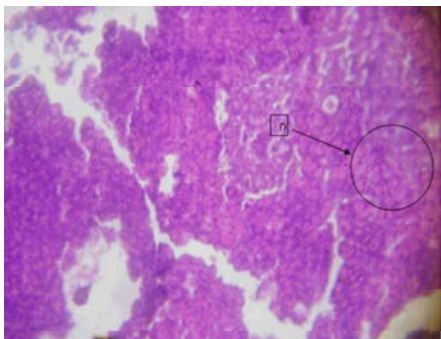
1.1: Control (No Degenerative changes)



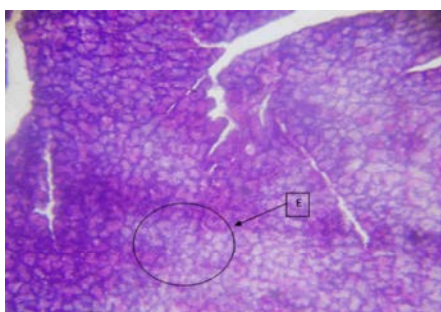
1.2: Diabetic control (Destruction of β-cell)



1.3: Glibenclamide (10 mg/kg) (Regeneration of β-cell)



1.4: EEAL (200 mg/kg) (Regeneration of  $\beta$ -cell)



1.5: EEAL (400 mg/kg) (Regeneration of  $\beta$ -cell)

## DISCUSSION

Disturbances in Glucose metabolism, altered lipid levels and Oxidative stress are important risk factors for diabetes, cardiovascular, oncologic and many other diseases [39].

In diabetic condition, elevated blood glucose, reduced body weight, polyuria, polydipsia and polyphagia are commonly observed. In present study, induction of diabetes by STZ-NA produced increase in blood glucose levels. This may be due to insulin deficiency or resistance state in diabetic control rats [40]. EEAL treatment significantly reduced blood glucose level in diabetic rats which represents reversal of insulin resistance or increasing insulin secretion possibly by regeneration of damaged pancreatic  $\beta$ -cells in STZ-NA induced diabetic rats. These effects may be attributed to either inhibition of increase in insulin output, inhibition of the intestinal absorption of glucose and increase in glucose metabolism because EEAL contains alkaloids, terpenoids, flavonoids, glycosides, polyphenols and tannins which have been proved to be antidiabetic activity by different mechanisms of action [13].

Hyperlipidemia is one of the major cardiovascular risk factor. Hyperlipidemia is a recognized complication of Diabetes mellitus characterized by elevated levels of

cholesterol, triglycerides, phospholipids and changes in lipoprotein composition. The results of present study indicated that EEAL has a lipid lowering effects on serum triglycerides, total Cholesterol, low-density lipoprotein and very low density lipoprotein of diabetic rats. EEAL treatment also increases the serum High-density lipoprotein level, which is involved in transport of cholesterol from peripheral tissues to liver and thereby it acts as a protective factor. So increased HDL levels helped in increased transport of peripheral tissue cholesterol to liver and thereby decrease blood cholesterol level.

Liver is the vital organ of metabolism, detoxification, storage and excretion of xenobiotics and their metabolites. SGOT and SGPT are reliable markers of liver function [41]. Treatment of the diabetic rats with EEAL and Glibenclamide caused reduction in the activity of these enzymes in serum compared to the diabetic untreated group and consequently alleviated liver damage caused by STZ-NA induced diabetes.

Numerous experimental and clinical observations have indicated that hyperglycemia may directly or indirectly contribute to an increased formation of free radicals and consequently to the onset of oxidative stress which has been implicated in diabetic complications. Oxidative stress is a condition of reduction in antioxidant enzymes like SOD, GSH and Catalase levels [44]. Recent studies showed that a number of plant products including polyphenolic substances (e.g. flavonoids and tannins) and various plant or herb extracts exert antioxidant actions [46]. In the present study, a decrease in Catalase levels was observed in the liver of diabetic control rats. Administration of EEAL produced antioxidant effect by increase in anti oxidative enzyme levels. Increased level of MDA observed in diabetic control rats. MDA, a marker of fatty chain peroxidation because high concentration of lipid was found to be present in liver of diabetic rats which results in the activation of NADPH dependent microsomal lipid peroxidation in liver. The treatment with EEAL decreased MDA level significantly in diabetic rats indicating protection against lipid peroxidation. The present study indicates that the antioxidant effect of EEAL may be due to inhibition of lipid peroxidation and increase in antioxidant enzymes.

Streptozotocin-nicotinamide induced diabetes is associated with the characteristic loss of body weight, which is due to increased muscle wasting and due to loss of tissue proteins. Diabetic rats treated with the EEAL showed an increase in body weight as compared to the

diabetic control, which may be due to its protective effect in controlling muscle wasting i.e. reversal of gluconeogenesis and may also be due to the improvement in insulin secretion and glycemic control. The results of the present investigation of EEAL showed significant antidiabetic activity, antihyperlipidemic and antioxidant properties against STZ-NA induced diabetic rats. Hence, EEAL may be regarded as a promising natural and safe remedy for prevention of diabetic complications.

### CONCLUSION

The results revealed that ethanolic extract of *Acacia leucophloea* stem bark possess significant antidiabetic, antihyperlipidemic and antioxidant activities in streptozotocin-nicotinamide induced type II diabetic rats. Further studies are necessary to elucidate in detail the mechanism of action of medicinal plant at the cellular and molecular mechanism. This extract also showed improvement in parameters like liver enzymes body weight.

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