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Research Article **Biochemistry**

Antidiabetic and hypolipidemic activity of *Terminalia bellirica* on alloxan induced Diabetic rats

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ABSTRACT

In the present study aimed to evaluate the antidiabetic and hypoglycemic activity of *Terminalia bellirica* owing biochemical parameters were analyzed. The animals were divided into six groups of six animals each as follows. Each animal was marked for identification and regularly monitoring. Group I-Vehicle control were injected with buffer alone (Non-diabetic) Group II Diabetic control. Group III *Terminalia bellirica* leaves extracts at a dose of 500mg/kg was orallygiven once a day for 20 days. Group IV Diabetic standard as 2.5mg/kg of Glibenclamide p.o was orally given once a day for 20 days. Administration of *Terminalia bellirica* to alloxan rats restored the level of glucose and lipid profile. This confirms the antidiabetic and hypolipidemic activity of *Terminalia bellirica*. The potential antidiabetic activity of *Terminalia bellirica* is due to the presence of phytochemical constitution present in plant. Some of these phytochemical such as Alkaloids, Flavonoids, Tannins, Saponin, Glycosides, Cardiac glycosides, Terpenoids and polyphenolic compounds have possessed antidiabetic activity.

Keywords: *Terminalia bellirica*, Alloxan, Lipid profile, Oxidative stress.

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INTRODUCTION

Diabetes is a metabolic disorder of carbohydrate, fat and protein, affecting a large number of population in the world (Pareek *et al*., 2009). Diabetes mellitus is not a single disorder but it is a group of metabolic disorder characterised by chronic hyperglycemia, resulting from defects in insulin secretion, insulin action, or both. Increased thirst, increased urinary output, ketonemia and ketonuria are the common symptoms. Diabetes mellitus has caused significant morbidity and mortality due to microvascular (retinopathy, neuropathy, and nephropathy) and macrovascular (heart attack, stroke and peripheral vascular disease) complications (Thévenod, 2008). Diabetes is mainly attributed to the rapid rise in unhealthy life style, urbanization and aging.

Hyperglycaemia which is the main symptom of diabetes mellitus generates reactive oxygen species (ROS) which cause lipid peroxidation and membrane damage. ROS plays an important role in the development of secondary complications in diabetes mellitus such as cataract, neuropathy and nephropathy. Antioxidants protect.-cells from oxidation by inhibiting the peroxidation chain reaction and thus they play an important role in the diabetes. Plants containing natural antioxidants such as tannins, flavonoids, vitamin C and E can preserve.-cell function and prevent diabetes induced ROS formation. Polyphenols, which are classified into many groups such as flavonoids, tannins and stilbenes, have been known as health-beneficial properties, which include free radical scavenging,and inhibition of hydrolytic,oxidative enzymes, anti-inflammatory action and antidiabetogenic potentiality (Patel *et al*., 2011). Aldose reductase as a key enzyme, catalyze the reduction of glucose to sorbitol and is associated in the chronic complications of diabetes such as peripheral neuropathy and retinopathy. Use of aldose reductase inhibitors and.-glucosidase inhibitors has been reported for the treatment of diabetic complications (Jung *et al*., 2011).

Many indigenous Indian medicinal plants have been found to be successfully used to manage diabetes. Plant drugs are frequently considered to be less toxic and free from side effects then synthetic ones. However, search for new anti-diabetic drugs continue. Keeping this view, the present study aimed to evaluate the anti diabetic and hypoglycemic activity of *Terminalia bellirica* owing biochemical parameters were analyzed.

MATERIALS AND METHODS

Collection of Plant materials:

The fully mature ***Terminalia bellirica*** leaves were collected from Tamil University in January 2015 at Thanjavur, Tamil Nadu, and South India.

Preparation of ethanolic leaf extract:

The collected ***Terminalia bellirica*** leaves were cut into small pieces and shade dried at room temperature. The ***Terminalia bellirica*** leaves were soaked with methanol (50%) for 48 hours. A semi solid extract was obtained after complete elimination of alcohol under reduced pressure. The extract contained both polar and non-polar phytocomponents of the plant material used. The extract was stored in refrigerator until used. The ***Terminalia bellirica*** leaves extract was dissolved in distilled water just before oral administration.

Preliminary phytochemical tests

The phytochemical test were carried out in the leaf extract of ***Terminalia bellirica*** using standard procedures to identify phytochemical constituents

Antidiabetic activity

Animals

Male albino rats of Wistar strain approximately weighing 180-190g were used in this study. They were healthy animals purchased from the Indian Institute of Science, Bangalore. The animals were housed in spacious polypropylene cages bedded with rice husk. The animal room was well ventilated and maintained under standard experimental conditions (Temperature 27 ± 2º C and 12 hour light/dark cycle) throughout the experimental period. All the animals were fed with standard pellet diet and water were provided *ad libitum*. They were acclimatized to the environment for one week prior to experimental use. The experiment was carried out according to the guidelines of the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA), New Delhi, India.

Chemicals:

Alloxan, Sodium hydroxide and Trichloro Acetic acid (TCAs) and diethyl ether were purchased for Sigma chemical company, Mumbai All other chemicals and reagents used in this study was of analytical grade with high purity and were obtained from Glaxo laboratories and Sisco Research laboratories, Mumbai, India.

Alloxan induced, Diabetic rats

NIDDM was induced in overnight fasted adult male Wistar albino rats weighing 150–200 g by a single intraperitoneal injection of 120 mg/kg alloxan monohydrate (Loba Chemie) (Mukhtar et al., 2004). This model has been used in earlier studies to induce type II diabetes in rats (Neeli et al., 2007). Glibenclamide (2.5 mg/kg) was used as the standard drug. After 72 h of alloxan injection, stable hyperglycemia was confirmed by estimating the glucose level in urine of rats by Benedict's qualitative test (Nagarajan et al., 2005). Plant extracts at a dose of 500mg/kg was orally given once a day for 15 days after hyperglycemia was confirmed by the elevated glucose levels in urine determined at 72 h.

The animals were divided into six groups of six animals each as follows. Each animal was marked for identification and regularly monitoring. Group I -Vehicle control were injected with buffer alone (Non-diabetic) Group II Diabetic control. Group III ***Terminalia bellirica*** leaves extracts at a dose of 500mg/kg was orallygiven once a day for 20 days. Group IV Diabetic standard as 2.5mg/kg of Glibenclamide p.o was orally given once a day for 20 days.

Collection of blood and preparation of serum sample

At the end of the experimental period, the animals were killed cervical dislocation after an overnight fasting. The blood sample was collected. The blood was allowed to clot by standing at room temperature for 30 minutes and then refrigerated for another 30 minute. The resultant clear part was centrifuged at 3000 rpm for 10minutes and then the serum (supernatant) was isolated and stored at refrigerated until required for biochemical analysis.

Biochemical estimation

Malondialdehyde was estimated by the thiobarbituric acid assay method of (Beuge and Aust 1978). Glucose was estimated by GOD/POD method (Trinder, 1969). Haemoglobin was estimated by Cyanmethaemoglobin method (Dacie and Lewis, 1968) (Beacon Diagnostic Kit). Serum Cholesterol was estimated by (Allain *et al*., 1974). Protein was estimated by the method of Lowry *et al.* (1951). Triglyceride was determined by the method of (Werner *et al.*, 1981). HDL cholesterol was estimated by the method of Allain *et al* (1974).

Low Density lipoprotein Cholesterol (LDL)

The reason for choosing LDL cholesterol as a target for lipid profile is that it represents the fraction of cholesterol, which is most deleterious and has been mostly directly correlated with clinical studies. This LDL cholesterol was calculated as per equation:LDL = [Total cholesterol] – [HDL Cholesterol] + [Triglycerides/5] LDL cholesterol levels were expressed as mg/dl serum.

Very Low Density Lipoprotein (VLDL)

The function of VLDL is to transport endogenously synthesized triglyceride and cholesterol into the peripheral tissue. VLDL cholesterol valus were calculated from the following formula suggested by equation:

VLDL = Triglycerides/5.

VLDL cholesterol levels were expressed as mg/dl serum.

Statistical Analysis:

Values were expressed as mean ± SD for six rats in the each group and statistical significant differences between mean values were determined by student " t" test and p< 0.05 were considered to be significant.

RESULTS

The present study was carried out on the plant sample revealed the presence of medicinally active constituents. The phytochemical characters of the ***Terminalia bellirica*** investigated a summarized in Table 1. The present study was carried out to evaluate the Antidiabetic activity of ***Terminalia bellirica*** on alloxan induced diabetic rats. The observations made on different groups of experimental animals were compared as follows.

Table I. Phytochemical screening of *Terminalia bellirica*

TEST	RESULT
Tannin	+
Phlobatannins	+
Saponin	+
Flavonoids	+
Steroids	++
Terpenoids	+
Triterpenoids	++
Alkaloids	+
Carbohydrate	+
Amino acid	++
Anthroquinone	+
Polyphenol	++
Glycoside	++

(+) Presence

Table 2. Represents the levels of Glucose and Hb in normal and experimental rats. Group II Diabetic rats showed a significant increased in the level of Glucose when compared to Group I rats. Group III and IV Diabetic rats treated with *Terminalia bellirica* and standard as glibenclamide significantly decreased in the level of Glucose when compared to group II. Group II Diabetic rats showed a significant decreased in the content of Hb when compared to Group I rats. Group III and IV Diabetic rats treated with *Terminalia bellirica* and standard as glibenclamide significantly increased in the level of Hb when compared to group II.

Table 2. Effect of *Terminalia bellirica* on Glucose and Hb in normal and experimental rats.

Parameters	Group I	Group II	Group III	Group IV
Glucose (mg/dl)	76.83±6.03	252.53±11.09*	86.43±3.52**	80.50±5.54**
Hb (gm/dl)	16.13±2.47	10.03±1.69*	12.30±4.06**	16.72±1.54**

Values were expressed as mean ± SD for six rats in each group.
* Significantly different from Group I ($P < 0.05$)
** Significantly different from Group II ($P < 0.05$)

Table 3. Represents the levels of MDA in serum of normal and experimental rats. Group II Diabetic rats showed a significant increased in the level of MDA when compared to Group I rats. Group III and IV Diabetic rats treated with *Terminalia bellirica* and standard as glibenclamide significantly decreased in the level of MDA when compared to group II.

Table 3. Effect of *Terminalia bellirica* on MDA and GSH in experimental rats

Parameters	Group I	Group II	Group III	Group IV
MDA (nmol /L)	1.32±1.14	5.83±1.19*	2.49±0.84**	2.26±1.07**

Values were expressed as mean ± SD for six rats in each group.
* Significantly different from Group I ($P < 0.05$)
** Significantly different from Group II ($P < 0.05$)

Table 4. Represents the levels of protein in serum of normal and experimental rats. Group II Diabetic rats showed a significant decreased in the level of protein when compared to Group I rats. Group III and IV Diabetic rats treated with *Terminalia bellirica* and standard as glibenclamide significantly increased in the level of protein when compared to group II.

Table 4. Effect of *Terminalia bellirica* on protein in experimental rats

Parameters	Group I	Group II	Group III	Group IV
Protein (gm/dl)	6.12±0.45	3.56±0.42*	5.17±0.44**	5.20±0.43**

Values were expressed as mean ± SD for six rats in each group.
* Significantly different from Group I ($P < 0.05$)
** Significantly different from Group II ($P < 0.05$)

Table 5. Represents the levels of cholesterol and triglyceride in serum of normal and experimental rats. Group II Diabetic rats showed a significant increased in the level of cholesterol when compared to Group I rats. Group III and IV Diabetic rats treated with *Terminalia bellirica* and standard as glibenclamide significantly decreased in the level of cholesterol when compared to group II. Group II Diabetic rats showed a significant increased in the level of triglyceride when compared to Group I rats. Group III and IV Diabetic rats treated with *Terminalia bellirica* and standard as glibenclamide significantly decreased in the level of triglyceride as compared to group II.

Table 6. represents the levels of LDL-cholesterol and VLDL -cholesterol in serum of normal and experimental rats. Group II Diabetic rats showed a significant increased in the level of LDL-cholesterol when compared to Group I rats. Group III and IV Diabetic rats treated with *Terminalia bellirica* and standard as glibenclamide significantly decreased in the level of LDL-cholesterol when compared to group II. Group II Diabetic rats showed a significant increased in the level of VLDL -cholesterol when compared to Group I rats. Group III and IV Diabetic rats treated with *Terminalia bellirica* and standard as glibenclamide significantly decreased in the level of VLDL -cholesterol as compared to group II.

Table 5. Effect of *Terminalia bellirica* on cholesterol and triglyceride in experimental rats

Parameters	Group I	Group II	Group III	Group IV
Cholesterol (mg/dl)	157.57±50.99	472.72±39.83*	121.20±4 4.03**	163.50±4 5.19**
Triglyceride (mg/dl)	180.93±33.40	402.37±4 0.82*	226.18±3 3.09**	190.47±3 3.40**

Values were expressed as mean ± SD for six rats in each group.
* Significantly different from Group I ($P < 0.05$)
** Significantly different from Group II ($P < 0.05$)

Table 6. Represents the levels of HDL-cholesterol in serum of normal and experimental rats. Group II Diabetic rats showed a significant decreased in the level of HDL -cholesterol when compared to Group I rats. Group III and IV Diabetic rats treated with *Terminalia bellirica* and standard as glibenclamide significantly increased in the level of HDL -cholesterol when compared to group II.

Table 6. Effect of *Terminalia bellirica* on HDL -cholesterol in experimental rats

Parameters	Group I	Group II	Group III	Group IV
HDL -cholesterol (mg/dl)	55.208±18.29	32.75±5.47*	70.83±12.9**	63.54±14.47**
LDL -cholesterol (mg/dl)	38.54±3.93	64.79±22.37*	40.25±4.02**	39.62±3.65**
VLDL -cholesterol (mg/dl)	36.18±6.68	80.47±0.16 *	45.23±6.61**	38.09±6.68**

Values were expressed as mean ± SD for six rats in each group.
* Significantly different from Group I ($P < 0.05$)
** Significantly different from Group II ($P < 0.05$)

DISCUSSION

Diabetes mellitus is one of the most common chronic diseases associated with carbohydrate metabolism. It is also an indication of co-morbidities such as obesity, hypertension, and hyperlipidemia which are metabolic complications of both clinical and experimental diabetes. Alloxan (AXN) is commonly used for experimental induction of type-I diabetes mellitus, which causes selective pancreatic islet beta cell cytotoxicity mediated through the release of nitricoxide (NO). This results in rapid reduction in pancreatic islet pyridine nucleotide concentration and subsequent beta-cell necrosis. This damages a large number of β cells, resulting in a decrease in endogenous insulin release, which paves the ways for the decreased use of glucose by the tissues. The action of AXN on mitochondria generates SOD anions, which leads to diabetic complications. Based on the above perspectives, in the present study, the oxidative stress has been assessed in rats made diabetic by AXN (Szkudelki 2001). Sulfonylureas such as glibenclamide are often used as a standard antidiabetic drug in AXN-induced diabetes to compare the efficacy of variety of antihyperglycemic compounds.

The ethanolic extract of *Terminalia bellirica* (Group III) was treated on Alloxan induced diabetic rats (Group II). The results were compared with control (Group I) and the positive control glibenclamide (Group IV) after 15 days of treatment based on biochemical parameters. After the Alloxan induction, glucose, lipid profiles, protein and Hb were restored to control level with the administration of the known drug glibenclamide and plant extracts of *Terminalia bellirica.*

Lipid peroxidation is attracting much attention in recent years due to its role in diseases process membrane lipids are particularly susceptible to lipid peroxidation due to the presence of polyunsaturated fatty acids. It has been implicated in the pathogenesis of a number of diseases and clinical conditions. These include atherosclerosis, cancer etc., Experimental and clinical evidence suggests that aldehyde products of lipid peroxidation can also act as bioactive molecule in physiological and pathological conditions. It is now generally accepted that lipid peroxidation and its product play an important role in liver, kidney, heart and brain toxicity (Lakshmi *et al*., 2005). Malondialdehyde (MDA) is the major aldehyde resulting from the peroxidation of biological membrane polyunsaturated fatty acid. MDA, a secondary product of lipid peroxidation is used as an indicator of tissue damage by series of chain reactions (Ray and Husain, 2002). MDA is one of the indicators of oxidative stress. In the present study, an increase in the levels of MDA was found and these levels were significantly reduced after the supplementation of the ethanol extract of *Terminalia bellirica* and glibenclamide. These indicate that, plant extract inhibit oxidative damage due to the antiperoxidative effect of ingredients present in ethanol extract of *Terminalia bellirica*. This could be correlated with previous study reported that *Cassia auriculata* flower (Pari and Latha, 2002) and *Tinospora cardifolia* (Prince *et al*., 1999) has antiperoxidative and antihyperlipidemic effect of diabetic animals.

In the present study, there was a significant elevation in glucose level in diabetic rats as compared with normal animals. *Terminalia bellirica* treated group exhibited significant reduction of glucose levels as compared to the diabetic control group. Over production of glucose by means of excessive hepatic glycogenolysis and gluconeogenesis is one of the fundamental basis of hyperglycemia in diabetes mellitus (Latner, 1958). The ability of *Terminalia bellirica* extract in effectively controlling the increase in blood glucose levels in the diabetic group of rats (Table 2) may be attributed to its antihyperglycemic activity.

The haemopoietic system is extremely sensitive to some environmental influences because of the rapid synthesis and destruction of cells with consequent heavy metabolic demands (Calistur, 2002). In the present study noted that lowered levels of total haemoglobin in AXN diabetic rats. During diabetes, the excess glucose present in the blood reacts with haemoglobin to form glycosylated haemoglobin. So the total haemoglobin level is lowered and glycosylated haemoglobin is increased in AXN diabetic rats (Sheela and Augusti, 1992). Administration of *Terminalia bellirica* reversed the total haemoglobin levels in AXN diabetic rats.

Almost all the plasma proteins except immunoglobulins are synthesized by the liver. Hence the measurement of serum proteins forms a reliable index of liver function. Serum total protein and albumin are quantitatively the most important protein synthesized by the liver and reflects the extent of functioning liver cell mass. A chronic disease of the liver is generally lowers serum total protein and albumin concentrations and hypoprotenemia (Mandal, 1992). A significant reduction in serum protein was observed in Alloxan induced diabetic rats (Group II), when compared to control (Group I) and glibenclamide treated rats (Group IV). On administration of ethanol extract of *Terminalia bellirica* to the diabetic rats, protein was found to be restored in normal. These results were in accordance with the effect of *Wattakaka volubilis* leaf in diabetic rats (Maruthupandian et al., 2000). The increased level of serum protein in Alloxan induced diabetic rats are presumed to be due to increased protein catabolism and gluconeogenesis during diabetes (Palanivel *et al*., 2001).

Diabetes affects not only the glucose metabolism and also affect the lipid metabolism (Sperling *et al*., 2000). The major effects of insulin in lipid metabolism are to increases lipoprotein lipase activity in adipose tissue and regulate the lipid metabolism. The insulin deficiency depletes the activity level of lipoprotein lipase, thus leading to deranged lipoprotein metabolism during diabetes (Ranganathan *et al.,* 2000). The lipoprotein levels in the AXN induced diabetic rats of the present study reveal a significant alter in lipoprotein metabolism.

The serum total cholesterol content increased significantly in diabetic animals. The elevated hypertriglyceridemia was increased in the synthesis of triglyceride rich lipoprotein particles (very low density lipoprotein, VLDL) in liver diminished catabolism in diabetic rats (Ginsberg, 1991). Since insulin has a potent inhibitory effect on lipolysis in adipocytes, insulin deficiency is associated with excess lipolysis and increased influx of free fatty acids to the liver (Ohno, 2000) The increased levels of low-density lipoprotein (LDL) and very low density lipoprotein (VLDL) in the diabetic animals might be due to over production of LDL and VLDL by the liver due to the stimulation of hepatic triglyceride synthesis as a result of free fatty acid influx (Coppack, 1994,). The high density lipoprotein (HDL) was significantly reduced in the diabetic rats which indicate a positive risk factor for atheroselerosis (Bopanna, 1997). Apart from the regulation of carbohydrate metabolism, insulin also plays an important role in the lipid metabolism. Insulin is a potent inhibitor of lipolysis, since it inhibits the activity of hormone sensitive lipase in adipose tissue and suppresses the release of free fatty acids (Loci *et al*., 1994). During diabetes, enhanced activity of the enzyme, increased lipolysis and releases more fatty acids into the circulation (Agardh *et al*., 1999).

The levels of serum TC, TG, LDL and VLDL were found to be significantly reduced in the *Terminalia bellirica* extracts treated diabetic animals. This might be due to the reduced hepatic triglyceride synthesis and or reduced lipolysis that might be due to the increase in serum insulin secretion in the *Terminalia bellirica* extract treated rats. The HDL increased significantly in the *Terminalia bellirica* extract treated rats indicating a reversed atherogenic risk.

Administration of *Terminalia bellirica* to AXN rats restored the level of glucose and lipid profile. This confirms the antidiabetic and hypolipidemic activity of *Terminalia bellirica*. The potential antidiabetic activity of *Terminalia bellirica* is due to the presence of phytochemical constitution present in plant. Some of these phytochemical such as Carbohydrates, Free amino acid, Alkaloids, Flavonoids, Tannins, Saponin, Quinones, Glycosides, Cardiac glycosides, Terpenoids and polyphenolic compounds have possessed antidiabetic activity.

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