ORIGINAL ARTICLE

Hypoglycemic effect of ethanolic extract of bark of *Terminalia arjuna* Linn. in normal and alloxan-induced noninsulin-dependent diabetes mellitus albino rats

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Introduction: The Bark of *Terminalia arjuna* Linn. (family-Combretaceae) is used in Indian Ayurvedic medicine for the treatment of diabetes mellitus. **Aim:** Therefore, the effect of ethanolic extract of bark of *Terminalia arjuna* on blood glucose level of normal and diabetic rats was evaluated in this study. **Materials and Methods:** Healthy Wistar albino rats (100-150 gm) were divided into four groups of six animals each. Normal control group received normal saline (10 ml/kg/day/p.o.); diabetic treated group received ethanolic extract of bark of *Terminalia arjuna* (500 mg/kg/p.o.); diabetic standard group received Glibenclamide (0.5 mg/kg/day/p.o.) given for 2 weeks. To induce diabetes, alloxan 150 mg/kg, i.p. single dose was administered to diabetic control, diabetic treated and diabetic standard groups. Blood glucose and body weight was estimated weekly for two weeks. For mechanism of action glycogen estimation on liver, cardiac and skeletal muscle; effect on adrenaline induced hyperglycemia and intestinal glucose absorption was done. For hypoglycemic action on normal rats, blood glucose was estimated at '0' min and '120' min. **Results:** The test drug showed significant decrease (P<0.01) in blood glucose level. The test drug showed a significant (P<0.01) increase in glycogen content in liver, cardiac and skeletal muscle, significantly (P<0.01) reduced adrenaline induced hyperglycemia and intestinal glucose absorption. Blood glucose in normal rats was significantly (P<0.01) decreased in drug treated groups. **Conclusion:** *Terminalia arjuna* bark possesses significant hypoglycaemic and anti-diabetic activity.

Key words: Antioxidant, blood glucose, flavonoids, glycogen

INTRODUCTION

Diabetes mellitus (DM) is a major health problem worldwide. Globally, the estimated incidence of diabetes and projection for year 2010, as given by International Diabetes Federation (IDF) is 239 million.[1]

Type 2 Diabetes mellitus is characterised by three pathophysiologic abnormalities: impaired insulin secretion, peripheral insulin resistance and excessive hepatic glucose production.[2]

Insulin and oral hypoglycemic are the most widely used drugs for diabetes but they have various side effects like hypoglycemia, weight gain (sulfonylureas), lactic acidosis (biguanides) and they may cause liver and renal damage.[3]

The management of diabetes without side effects is yet a challenge to the medical system. There is an increasing demand to use the natural products with antidiabetic activity. Plants are useful sources for the development of antidiabetic drugs.[1]

In the last few years, there has been an exponential growth in the field of herbal medicine and these drugs are gaining popularity both in developing and developed countries because of their natural origin and less side effects.[4]

Terminalia arjuna Linn. [Figure 1] belonging to the family Combretaceae is a large tropical woody tree distributed throughout India. It grows in tropical regions near rivers and streams. It is also planted as an ornamental tree and tree of shade. It is a cardiotonic and used for treating congestive cardiac failure and essential hypertention. It is also used in treating cirrhosis of liver, pulmonary tuberculosis, uterine disorders (leucorrhoea, menorrhagia and metrorrhagia), venereal diseases, epilepsy, chronic

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Figure 1: *Terminalia arjuna*

fever, nausea, diarrhoea, dysentery, urticaria, ulcers, fractured bones and diuresis.[5]

Bark of *Terminalia arjuna* (TA) is used in ayurveda in the treatment of diabetes mellitus.[5] Main chemical constitutes are tannins, triterpenoid saponins (arjunic acid, arjunolic acid, arjungenin and arjunic acid), flavonoids, gallic acid, ellagic acid and phytosterols.[6] Therefore, to validate the claim of the use of *Terminalia arjuna* in the treatment of diabetes mellitus in ayurveda, the present study were undertaken to evaluate the hypoglycemic and antidiabetic effect of ethanolic extract of bark of *Terminalia arjuna* in normal and alloxan-induced Noninsulin-dependent diabetes mellitus (NIDDM) albino rats.

MATERIALS AND METHODS

Drugs Used

Stem bark of TA were collected in the month of april-may from Assam Medical College and Hospital campus (AMCH), Dibrugarh and authenticated by Dr. M. Islam, Professor Department of Life Science, Dibrugarh University. A voucher specimen (No. DU/LS/209) was deposited at Dibrugarh University. Alloxan Monohydrate was obtained from Sigma Aldrich, Bangalore. Crude powder of glibenclamide and metformin was obtained from Aventis Pharma Limited, Goa.

Preparation of Plant Extract

The bark was washed thoroughly with distilled water, was air dried, powdered with electrical grinder and soaked in 90% ethanol for six hours in a tightly covered container. It is then transferred to a percolator with 90% ethanol and percolation is allowed to proceed slowly till the drug is completely exhausted. Ethanol is evaporated to a soft extract at a temperature not exceeding 60°C and is then transferred to a vacuum desicator.[7] A net yield of 30.6 gm was obtained by percolating 250 gm of dry powder of the bark (12.24%). The extract collected were stored in a air tight glass containers in a refrigerator at 2-8° C for use in the experiments.

Animals

Healthy albino rats of Wistar strain (100-150 gm) of either sex were used for the experiment. They were obtained from the central animal house, AMCH, Dibrugarh. The animals were housed in standard polypropylene cages and maintained under controlled room temperature (25 ± 5°C) and humidity (55 ± 5%) with 12:12 hrs light and dark cycle. The rats were fed with commercially available rat normal pellet diet and water *ad libitum*. Before commencing the work permission from the Institutional Animal Ethics Committee (Regd. No.634/02/a/CPCSEA) was obtained.

Acute Oral Toxicity Studies

Albino rats of either sex were used for acute oral toxicity test according to the OECD guidelines 425. A total of five animals were used which received a single oral-dose (2000 mg/kg body weight) of ethanolic extract of bark of *Terminalia arjuna* (EEBTA) after overnight fasting. After the administration of EEBTA, food was withheld for further 3-4 h. Animals were observed individually at least once during the first 30 min after dosing, periodically during the first 24 h (with special attention during the first 4 h) and daily thereafter for a period of 14 days. At the end of the study the animals were observed for general toxic signs, morphological behaviour and mortality.[8]

Study of Hypoglycemic Effect of EEBTA in Normal Rats

Three groups of animals (6 in each) were divided as follows:[9]

Normal control group:	Normal Saline; 10 ml/Kg/d orally
Test group:	EEBTA; 500 mg/Kg/d orally
Standard group:	Glibenclamide; 0.5 mg/Kg/d orally.[10]

All the rats were kept fasting for 18hours with free access to water before the experiment. Blood samples were collected from retro-orbital sinus after anaesthetising the animals. Glucose estimation was done at 0, 120 minutes after the above treatment by Glucose oxidase method.[11]

Experimental Design for Anti-Diabetic Study

A total of 30 animals were taken, 6 animals were taken as Normal control group. Rest of the animals (24) were used for induction of diabetes by a single intraperitoneal injection of alloxan monohydrate in the dose of 150 mg/Kg body weight. The fasting blood glucose determined after 72 hrs.[13] 18 rats showing blood glucose level >200 mg/100 ml were taken for the study. They (18) were divided as diabetic control, Diabetic Test and Diabetic Standard groups having 6 animals in each:[12]

Normal control: (Normal saline; 10 ml/Kg/d)
Diabetic control: (Normal saline; 10 ml/Kg/d)

Diabetic test: (EEBTA; 500 mg/Kg/d)

Diabetic Standard: (Glibenclamide; 0.5 mg/Kg/d) The above drugs were administered orally once daily for two weeks.

Blood glucose was estimated every week for 2 consecutive weeks. Blood samples were collected from orbital sinus of rats and blood glucose estimation was done by Glucose Oxidase Method. During the experimental period, the rats were weighed on day '0' and day '15' of the experiment and the change in body weights was compared.

Probable Mechanism of Antidiabetic Action

Glycogen estimation of liver, skeletal muscle and cardiac muscle

The rats were divided into four groups with six animals in each as before.

Normal control: (Normal saline; 10 ml/Kg/d)
Diabetic control: (Normal saline; 10 ml/Kg/d + Alloxan)
Diabetic test: (EEBTA; 500 mg/Kg/d + Alloxan)
Diabetic standard: (Glibenclamide; 0.5 mg/Kg/d + Alloxan)

After 2 hrs of administration of above drugs. The animals were killed by decapitation. The liver, leg muscle and heart tissues were taken out with care and their glycogen content was estimated by method described by Caroll *et al*., 1956.[14]

Effect on Adrenaline-induced Hyperglycemia

The rats were divided into three groups with six animals in each as before.

Normal control group: Normal saline; 10 ml/Kg/d
Test group: EEBTA; 500 mg/Kg/d
Standard group: Glibenclamide; 0.5 mg/Kg/d

The above drugs were administered orally after drawing fasting blood samples. Adrenaline hydrochloride 100 µg was administered intraperitoneally to all the rats one hour after drug administration. Blood samples were again collected half an hour later.[15]

Evaluation of Effect on Intestinal Glucose Absorption by Estimation of Glucose Uptake

The effect of EEBTA was studied by the method described by Das S (2001) with some modification. The modification being while Das S (2001) had made five to six intestinal loops of roughly equal size lying between proximal jejunum and distal iluem. In the present study an intestinal loop of 8cm from pyloric end was made.[16]

18 (eighteen) albino rats are to be taken and divided into 3 (three) groups containing 6 (six) animals in each group:

Control group: Normal; Saline 10 ml/Kg/d
Test group: EEBTA; 500 mg/kg/day.
Standard group: Metformin; 90 mg/kg p.o.[10]

The treatments were given for 7 days, following it animals were kept fasting for 18hrs. After that all animals were anaesthetized with thiopentone sodium 40 mg/kg i.p. and abdomen was opened through midline incision and intestinal loop of 8 cm from pyloric end was made. D-glucose 2.5 mg (1 ml of 250 mg% in normal saline at 37°C) was given in the loop by tuberculin syringe. Animals were sacrificed after 15 minutes and the intact loop was excised and weighed before and after draining the contents of loop to know the final volume. After constant dilution, resultant fluid was estimated for glucose content by glucose oxidase method.[11] The absorption was expressed in terms of mg/gm dry weight/hour. Dry weight of intestinal segment was measured after dehydrating the loop in ethyl alcohol for 24 hrs, and then drying in hot air oven at 110-120°C for 2 hrs.

Statistical Analysis

The statistical significance between groups was analyzed separately using One–way analysis of variance (ANOVA), followed by Dunnett's multiple comparison test. The body weights of the rats before (on '0' day) and after (on '15th' day) drug administration were compared using Student's '*t*' test (Paired). The significance was expressed by '*P*' values, as mentioned in the tables. '*P*' values of <0.05 were considered as significant.

RESULTS

Acute Toxicity Test

There was no mortality recorded among the rats at the dose of 2000 mg/Kg. Hence one-fourth of the dose tested i.e., 500 mg/kg body weight was selected for the study.

Effect on Fasting Blood Sugar Level

Normal rats

A significant (P<0.01) lowering of normal blood glucose was found in diabetic control and diabetic test when compared to normal control [Table 1]. The percentage reduction of blood glucose level in diabetic control and diabetic test was 17.17% and 27.27% respectively as compared to normal control.

Table 1: Effect of ethanolic extract of bark of *Terminalia arjuna* on blood glucose level of normal rats

Groups	Mean blood glucose level in mg%	
	'0 minute'	'120 minutes'
Normal control	102±2.53	99±2.00
Test	100±1.78	82±2.09[a]
Standard	101±2.60	72±2.82[a]
ANOVA		
f	1.098	204.5
df	2, 15	2, 15
P	>0.05	<0.01

Values are expressed as MEAN ± SEM; (n=6); One Way ANOVA followed by Dunnett's multiple comparison tests is done; [a]P<0.01 when compared to the normal control group

Diabetic rats

On repeated administration of the extract for 15 days, a significant (P<0.01) decrease in blood sugar was found in diabetic test and diabetic standard as compared to diabetic control which showed a significant (P<0.01) rise in blood sugar as compared to normal control [Table 2]. The percentage of reduction in blood glucose in diabetic test and diabetic standard was more on the 15th day (59.67% and 63.7% respectively) as compared to the 8th day (33.33% and 44.24% respectively).

Effect on Changes in Body Weight

Diabetic rats showed a decrease in body weight during the experimental period. This was significantly antagonized by the extract [Table 3].

Effect on Glycogen Estimation

There was a significant (P<0.01) increase in the glycogen content of liver, skeletal muscle and cardiac muscle in diabetic test and diabetic standard as compared to diabetic control which showed a significant (P<0.01) reduction in glycogen content in the above tissues as compared to normal control [Table 4]. The increase in glycogen content was more in diabetic standard than in diabetic test.

Table 2: Effect of ethanolic extract of bark of *Terminalia arjuna* on fasting blood glucose level of alloxan induced diabetic rats

Groups	Mean blood glucose level (mg/100 ml)			
	'0 day' (base line)	After 72 hours	'8th day'	'15th day'
Normal control	111±2.75	109±1.41	110±1.89	109±1.89
Diabetic control	110±2.6	296±2.82[a]	330±2.96[a]	372±2.66[a]
Diabetic test	110±2.44	330±3.28[b]	220±2.19[b]	150±3.i6[b]
Diabetic standard	112±2.09	371±3.4[b]	184±2.82[b]	135±2.68[b]
ANOVA				
f	0.887	9980	7991	1266
df	3, 20	3, 20	3, 20	3, 20
P	>0.05	<0.01	<0.01	<0.01

Values are expressed as MEAN±SEM; (n=6); one way ANOVA followed by Dunnett's multiple comparison tests is done; [a]P<0.01 when compared to the normal control group; [b]P<0.01 when compared to the diabetic control group

Table 3: Effect of ethanolic extract of bark of *Terminalia arjuna* on body weight in alloxan induced diabetic rats

Groups	Initial ('0' day)	Final (15th day)	Change	% of increase	% of decrease
Normal control	120±2.28	125±3.16[a]	5±0.89	4.16	
Diabetic control	122±1.78	101±2.28[a]	21±1.41		17.21
Diabetic test	121±2.00	135±2.27[a]	14±1.25	11.57	
Diabetic standard	120±2.6	136±1.41[a]	16±1.26	13.33	
ANOVA					
f	1.146	283.8	178.7		
df	3, 20	3, 20	3, 20		
P	>0.05	<0.01	<0.01		

Values are expressed as MEAN±SEM (n=6); ANOVA followed by student's t-test (paired) test is done; [a]P<0.01, when compared to the initial body weight ; (weights in gms.)

Effect on Adrenaline-Induced Hyperglycemia

Hyperglycemic response was seen after half an hour of adrenaline injection. The test drug and the standard drug significantly (P<0.01) reduced hyperglycemia induced by adrenaline [Table 5]. The percentage of reduction of blood glucose was 35.91% and 51.47% respectively in the test and standard group as compared to control group.

Effect on Intestinal Glucose Absorption

The test and standard group showed significant (P<0.01) reduction in intestinal glucose absorption as compared to normal control group [Table 6]. The reduction in absorption was more in the standard group than in the test group.

Table 4: Effect of ethanolic extract of bark of *Terminalia arjuna* on glycogen concentration in liver, skeletal muscle and cardiac muscle

Groups	Glycogen concentration (mg/100 gm)		
	Liver	Skeletal muscle	Cardiac muscle
Normal control	48±2.19	30±3.3	35±1.96
Diabetic control	26±1.66[a]	13±1.17[a]	17±1.89[a]
Diabetic test	44±2.19[b]	24±1.92[b]	29±1.99[b]
Diabetic standard	46±1.84[b]	27±2.53[b]	32±3.02[b]
ANOVA			
f	156.4	58.91	72.66
df	3, 20	3, 20	3, 20
P	<0.01	<0.01	<0.01

Values are expressed as mean±SEM (n=6); ANOVA followed by Dunnett's multiple comparison tests is done; [a]P<0.01, when compared to the normal control group; [b]P<0.01, when compared to the diabetic control group

Table 5: Effect of ethanolic extract of bark of *Terminalia arjuna* on adrenalin-induced hyperglycemia in albino rats

Group	Blood glucose level (mg%)				
	'0 hour' fasting	½ hour after adrenalin	Change	% of increase	% of decrease
Normal control	103±2.09	199±2.00	96±2.36	93.20	
Test drug	105±1.54	177±2.28[a]	72±2.19[a]	68.57	35.91
Standard drug	104±1.67	168±2.44[a]	64±2.75[a]	61.53	51.47
ANOVA					
f	1.875	301.2	277.3		
df	2, 15	2, 15	2, 15		
P	>0.05	<0.01	<0.01		

Values are expressed as MEAN±SEM; (n=6); one way ANOVA followed by dunnett's multiple comparison tests is done; [a]P<0.01 when compared to the normal control group

Table 6: Effect of ethanolic extract of bark of *Terminalia arjuna* on intestinal glucose absorption

Groups	Glucose absorption (mg/gm dry wt/hr)
Normal control	94±2.09
Test	71±1.78[a]
Standard	65±2.96[a]
ANOVA	
f	257.2
df	2, 15
P	<0.01

Values are expressed as MEAN ± SEM; (n = 6); One Way ANOVA followed by Dunnett's multiple comparison tests is done; [a]P<0.01 when compared to the normal control group

DISCUSSION

In diabetic patients, glycation reaction occurs in various tissues, including the β-cells of pancreas, resulting in the formation of ROS (reactive oxygen species). These ROS produced may play a role in the development of diabetes related complications.[17] Antioxidant treatment has beneficial effects on preservation of β-cell function in diabetes.[17] Alloxan, a cytotoxic agent induces chemical diabetes (alloxan diabetes) in a variety of animal species through damage to insulin secreting cells. Alloxan diabetes is due to destruction of islets of langerhans of the pancreas. After administration, it is rapidly and selectively taken up by the β-cells of the pancreas, following which there is formation of redox cycle for the generation of ROS, superoxide radicals and hydrogen peroxide.[18] The reactive oxygen species, so produced, induce DNA cleavage and protein fragmentation of pancreatic islet cells leading to cell death and apoptosis.[17]

Plants which contain the active principles like glycosides, alkaloids, terpenoids, flavonoids etc., have antioxidant activity and are claimed to possess antidiabetic effects.[19] Flavonoids are known to regenerate the damaged β-cells in the alloxan induced diabetic rats.[20] Plant polyphenolics and saponin inhibit glucose transport across the intestine by inhibiting sodium glucose co-transporter-1 (S-GLUT-1).[21] Bark of *Terminalia arjuna* contain strong antioxidants (flavones, tannins, oligomeric proanthocyanidines), glycosides (argentine arjunoside I-IV), acids (arjunic acid, terminic acid).[22] Triterpene carboxylic acid (terminoic acid), β-sitosterol and saponin.[23]

In the present study, it was seen that EEBTA significantly lowered the blood sugar level in diabetic rats. It may have exerted its antidiabetic effect by its antioxidant activity due to the presence of the phytochemicals (flavonoids, tannins, glycosides, alkaloids, terpenoids) in it which are strong antioxidants. Moreover, due to its flavonoids content it may have regenerated the damaged β-cells of the pancreas. It may also be due to the presence of some phytocchemicals which has got insulin-like action.

Diabetic rats treated with the test and standard drug showed a significant increase in body weight on the 15th day when compared to the initial body weight on the 0th day, whereas in the diabetic group there was a significant decrease as compared to the normal control group. This may also be due to its insulin-like and insulin releasing action which prevented lyolysis and muscle protein breakdown, thereby causing increase in the body weight.

In type 2DM patients, due to insulin deficiency, there is impairment in glycogen synthase activation in the skeletal muscle due to inability of insulin to phosphorylate IRS-1, causing decreased activation of the enzyme PI-3 K (phosphatidylinositol 3-kinase), leading to decreased expression and translocation of GLUT-4 glucose transporters.[24] EEBTA due to its insulin-like action of its phytochemicals probably increased PI-3 K activation leading to stimulation of muscle glycogen synthase. The increase in glycogen concentration in skeletal and cardiac muscle might also be due to increased expression and translocation of GLUT-4 glucose transporters as a result of increased activation of PI-3 K, leading to increased peripheral glucose uptake. The increase in `liver glycogen content due to increase in synthesis of glycogen synthase in alloxan induced diabetic rats has been reported.[25] Therefore, the increase in liver glycogen content caused by EEBTA may also be due to increased synthesis of liver glycogen synthase enzyme.

The test drug was also significantly reduced the adrenaline-induced hyperglycemia probably by inhibiting adrenaline induced stimulation of α_2 receptors in β-cells of pancreas and thus promoting further insulin release.[26]

EEBTA also significantly reduced the glucose absorption as compared to the control group. The rate of absorption of glucose in EEBTA treated group was comparable to the standard drug metformin. This mechanism may be due to the presence of saponin which inhibit glucose transport across the intestine by S-GLUT-1 mentioned above.

CONCLUSION

From the above study it can be concluded that ethanolic extract of bark of *Terminalia arjuna* at the dose of 500 mg/kg body weight produced significant hypoglycemic effect in normal albino rats as well as significant antidiadetic effect in alloxan induced NIDDM albino rats. Though extensive work has been undertaken to work out the mechanism by which EEBTA could be exerting its effects, it is still not clear. However, probable hypothesis that may be involved in the therapeutic action of *Terminalia arjuna* can be considered here.

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