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Lipid Lowering Effect of Methanol Extract of *Tamarixaphylla*L. Karst (Saltcedar) in Streptozocin-Nicotinamide Induced Diabetic Rats

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Abstract

The pervasiveness of Diabetes Mellitus is increasing worldwide and it is becoming a most important socioeconomic concern. Diabetes Mellitus is a complex multi-factorious disorder that alter the metabolism of chief macromolecules like proteins, fats and carbohydrates.Plants having therapeutic properties play significant role in the management of DM particularly in developing countries. *Tamarixaphyll*a has been used commonly in Pakistan to treat various disorders. *Tamarixaphylla* leaves extract was administered to Streptozotocin (STZ) + Nicotinamide (65mg/kg+180mg/kgbw) induced diabetic male Wistaralbinoratsat various doses i.e. (100, 250, 400 mg/kg body weight) for a duration of 21 days. Plasma glucose concentration was reduced markedly ($p < 0.05$) in a dose dependent pattern when was related to the control rats. In addition, IP administration of *Tamarixaphylla* leaves extract (250, 400 mg/kg body weight) evidently reduced serum total cholesterol, LDL-cholesterol, triglyceride and at the same time distinctly improve HDL-cholesterol level in serum when compare with diabetic control rats. Results of this experimentally designated study shows that *Tamarixaphylla* leaves extract possesses Antihyperglycemic and Antihyperlipidemic effect and hence it could be used as antidiabetic drug for treatment of diabetes and its alliedcomplications.

Keywords: Antihyperlipidemic; Diabetes; Streptozocin; Tamarixaphylla

Introduction

Diabetes mellitus is the biggest endocrine disorder in the world of having multiple causes, involving alter metabolism of macromolecules like carbohydrate, fat and protein. Almost all forms of diabetes mellitus are either due to a decline in the circulating level of insulin (insulin deficiency) or a decline in the sensitivity of peripheral tissues to insulin action (insulin resistance) or both [1]. The long-term hyperglycemia of diabetes is accompanied with failure of multiple organs i.e. heart, and blood vessels nerves, kidneys and eyes. A number of pathological progressions are involved in the development and advancement of diabetes mellitus i.e. insulin deficiency due to auto immune destruction of beta cells of pancreas [2]. Conferring to a report of WHO that current approximation of diabetic patient around the globe is 220 million and this is going to be doubled till 2030[3].

The overall goal of all diabetes treatment and its management is based on oral antihyperglycemics and insulin. Four main classes of oral hypoglycemic agents that are widely used are Sulphonylureas, biguanides, thiazolidinedione's and alpha glucosidase inhibitors. Each among these classes of drugs act contrarily involving different mechanism of actions i.e., potentiating insulin discharge from beta cells, inhibition of hepatic gluconeogenesis, enhancing insulin receptor sensitivity and postponing digestion and absorption of carbohydrates correspondingly. However, the use of oral antihyperglycemics has been limited by the accompanied side effects i.e.,hematological, cutaneous and gastrointestinal reactions, hypoglycemic shock and damaging liver and kidneys function. In addition, they are not harmless to be used in prenatal period [4]. Thus, it is essential to search for new and if conceivable more effective drugs and this could be possible by the massive reservoir of phytochemicals [2].

Naturehasdelivereduswithanumbermedicinaltreatmentsforthousandsofyearsand phytochemical centered system is still play-

ing a significant role in principal health care system of almost 80% of underdeveloped and developed countries of the world. Most of the existing marketed medicines are either distillations, combinations, reproductions and variations of ingredients that are originated in nature [1]. Lately,interestisrisingin herbal medications due to absence of side effects that are very highly related with current therapeutic agents used for the treatment of diabetes. A number of research investigators have confirmed that coumarins, flavonoids. Terpenoids, and other plant secondary metabolites including arginine and glutamic acid has antidiabetic properties [4]. The World Health Organization (WHO)has suggested that plants having antihyperglycemic effects may offer us with an alternative source of new antidiabetic drugs that can be formulated into new pharmaceutical entities, or may be used simply as dietetic adjunct with currenttherapies[5].

Tamarixaphylla. L Karst (Tamaricaceae) is the leading known species of tamarix (attaining a height of approx. 18 metres-60 feet.). This species has been named with a no of common names including Athel tamarisk, Athel tree, Athel pine and Saltcedar. It is a perennial tree, native habitation is Central, East and North Africa. The phytochemical screening of the plant reveals existence of tannins in all extracts while absenceofalkaloids.Othermetabolitesandbiologicallyactivecompoundsrecognized were flavonoids, cardiac glycosides, steroids and terpenoids[6]. T.aphylla is practice as herbal medications such as diuretic, carminative, anti-inflammatory and for treatment internal hematomas[7] tuberculosis, leprosy, smallpoxaphrodisiacandtonic, hepatitis, eczema and other skin ailments[8]. While it is scientifically authenticated as an Analgesic and Antipyretic [9] Antimicrobial [10] Antifungal [11]and have cardio- protective effect in Doxorubicin induced cardiotoxicity[12].

Although TamarixAphylla L. Karst has been examined for its various medicinal properties. However, there was no documented reports on the anti-hyperglyemic and antilipidemic activity of this plant. So, this study was undertaken for the purpose to evaluate the antidiabetic and antilipidemic activity of methanol extract of TamarixaphyllaL. Karst in Streptozocin-Nicotinamide induced diabetic rats.

Materials and Methods

Kits and Chemicals

Streptozocin was procured from M.S. Traders local Distributor of Sigma Aldrich Lahore Pakistan. All biochemical parameters were performed on Microlab 200 Semi- Automatic Chemistry Analyzer using DiaSys Reagents kits. Abbott Free Style Optium Glucometer was used for the measurement of Fasting Blood Sugar of rats. Glibenclamide and the rest of chemicals were gained from local firms (Pakistan) and were of analytical grade.

Plant Material and Extraction

Fresh green Leaves were taken from the tree of *Tamarixaphylla*L. Karst in the month of April 2015 from Bajaur Agency,(FATA), Pakistan, Dr. Barkat in the Department of Botany, University of Peshawar, Khyber PukhtoonKhwa botanically identified and authenticate the plant and a voucher specimen (No.20089 PUP) was put at the herbarium of Botany Department. The leaves of the plant were shadow dried at 30-35°C and the dried leaves were crushed into coarse powder with auto-mix blender. The powder gained (3.24 kg) was soaked in 5 L/kg of the extract in 80% methanol for 14 days at room temperature with daily stirring and mixing. The filtrate was then concentrated for confiscating of extraction solvent under reduced pressure at 40 ◦C.At the end a dark green soluble crude residue was achieved (about 214.27 g, 6.61%w/w). Normal Saline was used for the dissolution of the extract for experimentation purposes.

Experimental Animals

50 Male Wistar albino rats of age 8-10 weeks old and weighing 220-320 g were used in this Study. All rats were obtained from National Institute of Health (NIH), Islamabad, Pakistan. All rats were retained in a well-ventilated room having temperature (25˚C ± 2˚C) and humidity (40-50%) in 12 hrs. light-dark cycle. Rats were fed on normal laboratory food and were allowed free access to water for two weeks before starting and during the experimental period. This experimental was performed bases on the guidelines set by the Animal Ethics Committee, Institute of Basic Medical Sciences, Khyber Medical University, Pakistan.

Induction of Diabetes in Experimental Rats

Rats were kept starved overnight for 12-h before injection administration. Single Streptozocin injection (65 mg/kg Body Weight (b.w.)) was used for the induction of diabetes in rats. It was dissolved in freshly ice-cold saline for the purpose of injection [13]. Control animals were given an injection of an equivalent volume of normal saline alone, Nicotinamide dissolved in normal saline (180 mg/kg, i.p) was administered 15 mins before STZ administration [14]. To overcome hypoglycemia caused by STZ 10% glucose solutions was given after 6-hr of administrations of STZ for a period of 24-hr [2]. After induction of diabetes rats with moderate diabetes (i.e. fasting blood glucose concentration, >200 mg/dl) was selected for furtherexperimentation.

Acute Toxicity Studies

Seven groups were made containing six rats in each group. Healthy male rats were divided into vehicle treated (control) and extract treated (test) groups, respectively. *Tramarixaphylla* was administered to test group intraperitoneally at dose rangedfrom 500-2100 mg/kg. while only normal saline was used for the treat-

ment of control group [13]. For 2 hour rats were continuously kept under observation for

- Neurological profile: Neurological profile: spontaneous activity, reactivity, touch response, pain response, and gait, pain response, spontaneous activity, reactivity and touchresponse.
- Behavioralprofile: fearfulness irritability, restlessness, and alertness.
- Autonomic profile: urination and defecation.

Death or lethality was observed after 24 hour.

Experimental Design

Total no of Wister rats used in the experiments were 42. These animals were divided into 7 groups each containing six animals as follow.

- Group I: Control rats
- Group II: Negative control group (Diabetes induced by Streptozocin)
- Group III: Diabetes induced rats treated with *T.aphylla* leafextract (100mg/kg/day) for 21days
- Group IV: Diabetes induced rats treated with *T.aphylla* leafextract (250mg/kg/day) for 21days
- Group V: Diabetes induced rats treated with *T.aphylla* leaf extract (400mg/kg/day) for 21days.
- Group VI: Diabetes induced rats treated with glimepride (5mg/kg/day) for 21days
- GroupVII: Normal rats treated with *T.aphylla* leaf extract (250mg/kg/day) for 21 days.

Body weights of the animals used in the experiments were measured both in the start and at the end of the experiments. Glucose level in the blood was monitored at a regular interval. After experiments animals were anesthetized beforedecapitation.

Phytochemical Screening

The phytochemical analysis showed presence of tannins, terpenoids, steroids, flavonoids and cardiac glycosides. But alkaloids, saponins and cyanogen's glycosides were absent [7] (Table 1).

Metabolite	W.	W-E.	W-M.	W-A.
	Extract	Extract	Extract	Extract
Steroids	+	+	+	+
Terpenoids	+	+	+	+
Alkaloids	-	-	-	-
Flavonoids	+	+	+	+
Tannins	+	+	+	+
Cardiac glycosides	Tr	+	+	+
Cyanogens glycosides	-	-	-	-
Free quinines	-	-	-	-
Anthraquinones	+	-	-	-
Saponins	-	-	-	-
Reducing sugar	+	-	-	-
Gum	tr	-	-	-

tr: trace, W: Water (100%), W-E: Water-Ethanol (30-70; v-v) W-M: Water-Methanol (30-70; v-v) W-A: Water-Acetone (30-70; v-v).

Table 1: Phytochemical Compounds Identified in Different Extracts.

Biochemical Parameters

Blood glucose was measured with e glucometer (Abbott FreeStyle Optium, England) onday0,3,7,14and21,respectively. Ratswereanesthetizedbeforecollectionofblood by cardiac puncture. Both in normal and Streptozocin-nicotinamide induced diabetic rat's LDL, HDL, triglycerides and cholesterol was elevated. Serum biochemistry parameterslikecholesterol, triglycerides, HDL, LDL were performed on Microlab 200 Semi-Automatic Chemistry Analyser using DiaSys Reagents kits[14].

Statistical Analysis

Results were expressed as mean ± SD of six animals per group. SPSS20.0 software was used for statistical analysis. Hypothesis testing methods included one-way ANOVA followed by LSD test. P-values < 0.05 were considered assignificant.

Results

Acute ToxicityTests

In acute toxicity study, Methanol Extract of T*amarixaphylla* applied animals did not indicate any alteration in their behavioral pattern. Healthy male rats were used for the experiments. Mortality rate was zero in the treated group and behavior seemed to be normal. There was no change in the blood sugar concentration of the normoglycemic rats. Till 1500 mg/kg dose no toxic reaction or death wasencountered.

Effect *Tamarixaphylla* of on Body Weight

(Table 2) show the outcome of *Tamarixaphylla* on body mass of normal and STZ- NIC prompted diabetic animals. The STZ-NIC induced animals showed decrease in body weight (-6.41%) compared to standard control animals. I.P administration *Tamarixaphylla* of (400 mg/kg body weight) for 21 days significantly increased (+4.99) body weight of diabetic mice matched to diabetic control animals shown in (Figure 1).

Groups	Body Weights	
	0 Day (g)	21st Day (g)
Normal control	263.3 ± 5.6	315.6 ± 6.7a
Normal+*Tamarixaphylla*250mg/kg body weight	254.4 ± 7.2	297.6 ± 8.4
Diabetic control	257.3 ± 7.3	241.8 ± 6.8b
Diabetic+*Tamarixaphylla*100 mg/kg body weight	267.6 ± 7.6	254.2 ± 7.2
Diabetic+*Tamarixaphylla*250 mg/kg body weight	262.2 ± 7.4	264.8 ± 7.5
Diabetic+*Tamarixaphylla*400 mg/kg body weight	256.5 ± 7.3	269.3 ± 7.6a
Diabetic+glibenclamide 5mg/kg bodyweight	259.9 ± 7.4	283.2 ± 8.0a
Each value is mean ± SD for six rats in each group		

Table 2: Effect of *Tamarixaphylla* on Body Weights in STZ-NIC Induced Diabetic Rats.

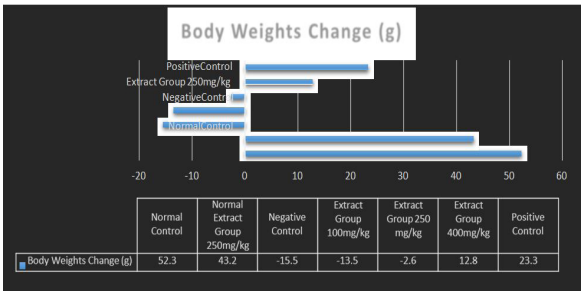

Figure 1: Effect of *Tamarixaphylla*on Body Weights in STZ-NIC Induced Diabetic Rats.

Effect of *Tamarixaphylla*on Fasting BloodGlucose

Glucose level in the blood was measured in test and control animals on days 0,3,7,14 and 21, respectively. Comparing to normal rat's glucose level in the blood of STZ-NIC induced diabetic rats was significantly high (Figure 2). I.P administration of *Tamarixaphylla* (400mg/kg body weight) lead to a significant decrease in fasting blood glucose level matched to diabetic control (Table3).

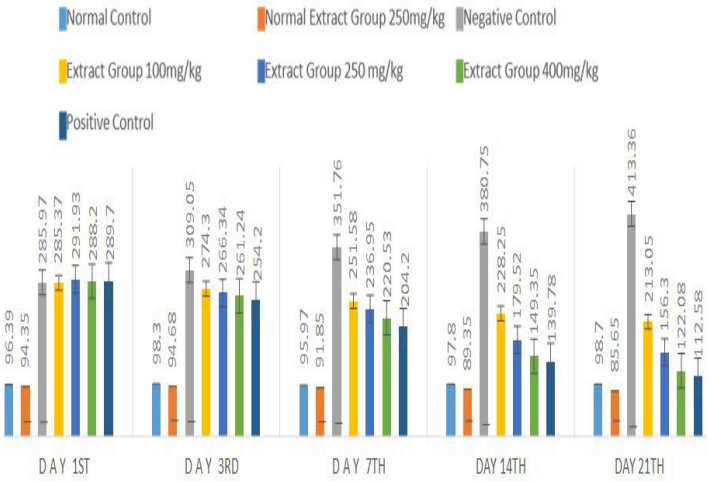

Figure 2: TamarixAphyllaEffect on FBS in STZ-NIC induced diabetic rats.

Groups	Fasting Blood Glucose				
	1st Day (mg/dl)	3rd Day (mg/dl)	7th Day (mg/dl)	14th Day (mg/dl)	21th Day (mg/dl)
Normal control	96.3 ± 6.1	98.3 ± 6.9	95.9 ± 6.8	97.8 ± 6.9	97.8 ± 6.9a
Normal+*Tamarixaphylla* 250mg/kg body weight	94.3 ± 6.3	94.6 ± 7.1	91.8 ± 7.4	89.3 ± 6.6	85.6 ± 7.5
Diabetic control	285.9 ± 9.9	309.0 ± 13.8	351.7 ± 19.2	380.7 ± 17.9	413.3 ± 24.4b
Diabetic+Tamarixaphylla 100 mg/kg body weight	285.3 ± 9.1	274.2 ± 6.8	251.5 ± 8.8	228.2 ± 6.1	213.0 ± 6.5
Diabetic+*Tamarixaphylla*250 mg/kg body weight	291.9 ± 8.6	266.3 ± 6.5	236.9 ± 4.9	179.5 ± 8.4	156.6 ± 5.7
Diabetic+*Tamarixaphylla*400 mg/kg body weight	288.2 ± 8.1	261.2 ± 4.2	220.5 ± 6.8	149.3 ± 11.2	122.0 ± 9.4a
Diabetic+glibenclamide 5mg/kg bodyweight	289.6 ± 9.7	254.2 ± 11.3	204.5 ± 7.4	139.7 ± 9.8	112.58 ± 9.5a
Each value is mean ±SD for six rats in each group.					

Table 3: Effect of *Tamarixaphylla* on Fasting Blood Glucose in STZ-NIC-Induced DiabeticRats.

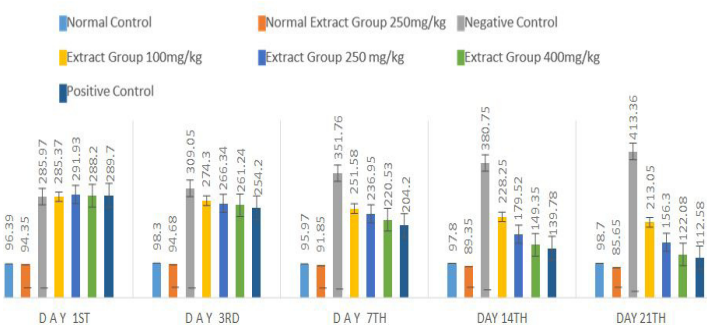

Figure 2: *Tamarixaphylla* Effect on FBS in STZ-NIC Induced Diabetic Rats.

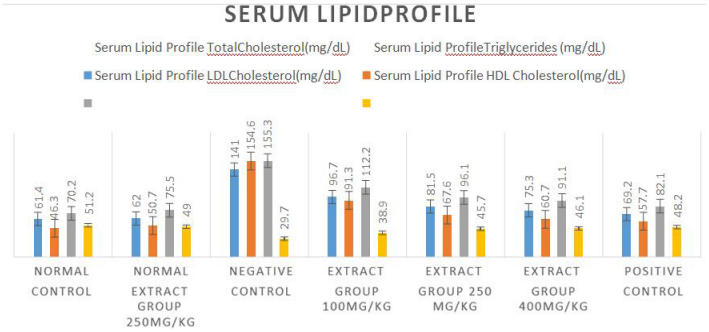

Figure 3: Effect of *Tamarixaphylla*on Serum Lipid Profile in STZ-NIC Induced Diabetic Rats.

Effect of *Tamarixaphylla*on Lipid Profile

(Table4) shows the action of *Tamarixaphylla* on overall triglycerides, cholesterol, HDL-cholesterol and LDL-cholesterol in standard control, diabetic control rats and tested group. Administration of *Tamarixaphylla* for 21 days reduced the entire cholesterol, triglycerides and LDL-cholesterol levels and amplified HDL-cholesterol significantly when paralleled to diabetic control rats (Figure 3).

Groups	Serum Lipid Profile			
			LDL	HDL
	Total Cholesterol (mg/dL)	Triglycerides (mg/dL)	Cholesterol (mg/dL)	Cholesterol (mg/dL)
Normal control	61.4 ± 5.0a	46.3 ± 3.1a	70.2 ± 4.2a	51.2 ± 4.2a
Normal+*Tamarixaphylla* 250mg/kg body weight	62.0 ± 4.9	50.7 ± 3.4	75.5 ± 4.3	49.0 ± 3.7
Diabetic control	141.0 ± 8.1b	154.6 ± 7.7b	155.3 ± 9.2b	29.7 ± 3.2b
Diabetic+*Tamarixaphylla* 100 mg/kg body weight	96.7 ± 6.4	91.3 ± 6.3	112.2 ± 7.14	38.9 ± 3.2
Diabetic+*Tamarixaphylla*250 mg/kg body weight	81.5 ± 4.7a	67.6 ± 3.93a	96.1 ± 6.5a	45.7 ± 3.6a
Diabetic+*Tamarixaphylla* 400 mg/kg body weight	75.3 ± 4.4a	60.7 ± 3.8a	91.1 ± 6.4a	46.1 ± 3.5a
Diabetic+glibenclamide 5mg/kg bodyweight	69.2 ± 4.4a	57.7 ± 3.8a	82.1 ± 4.5a	48.2 ± 3.9a
Each value is mean ± SD for six rats in each group.				

Table 4: Effect of Tamarixaphyllaon Serum Lipid Profile in STZ-NIC Induced DiabeticRats.

Discussion

Diabetes arises from destruction of B-cell due to the toxic effect of STZ, which helps preferential uptake into pancreatic B-cells over GLUT2. There is clear evidence that free radicals play vital role in the mechanism of DNA impairment and cytotoxicity by STZ. It has been stated that STZ initiate free radical's generation by the xanthine oxidase system of pancreatic cells, and enhances H2O2 production. As result, it leads to DNA fragmentation and necrosis in the pancreatic B-cell islets. Therefore, the rate of insulin synthesis is reduced. B- cells function is protected by injecting NA, a poly -ADP-ribose synthetase inhibitor. Actually, it inhibits insulin secretion by reduction in the level of NAD (nicotinamide adeninedi nucleotide. Thereby inhibition of insulin secretion is partially reversed and this prevents exacerbation of experimental diabetes after administration ofSTZ.

This circumstance contributes a number of characteristics similar to type 2 diabetes mellitus[15]. In present study, elevated blood glucose level and decrease insulin level were observed in STZ-NA induced diabetic rats. We can assume that it follows the above-mentioned mechanism of action of STZ. *Tamarixaphylla*, 250 mg/kg, 400mg/kg and glibenclamide 5mg/kg reduced glucose level in the blood of diabetic rats from first to fourth week compared with diabetic control rats. Therefore, the hypoglycemic action of *Tamarixaphylla* might be due to its protective action against STZ-mediated obliteration to the pancreatic beta cells and also perhaps because of production of impaired beta cell or increased insulin discharge.

Due to rapid muscle proteolysis, muscle degeneration occurs resulting in loss of body cell mass. Protein production is controlled by insulin, its absence results muscle loss. The unrestrained diabetes is linked to severe muscle wasting [16]. In current study, STZ-injected diabetic rats exhibited weight loss matched to control rats. Both *Tamarixaphylla* and glibenclamide inhibited weight loss

in diabetes induced rats and showed increase in the body weight when matched to diabetic control rats. This effect may be due to its inhibitory action on pancreatic beta cells destruction by STZ, increasing blood insulin level and thus inhibit muscleloss.

Hyperglycemia is one of the major cause of Cardiovascular Diseases (CVD). Research revealed on animals showed that hyperglycemia assist glycation and peroxidation of proteins resulting in damage to the arterial walls [17]. In comparison to non-diabetic individuals, chance of cardio vascular disease is 2-8 folds higher in diabetic individuals. Coronary Heart Disease (CHD) is one of the principal cause of morbidity and mortality in diabetic individuals [18]. Both type of diabetes i.e. type I and II are independent risk for CHD [19]. The vascular illnesses which occur in diabetes is due to problem in lipoprotein metabolism, resulting in progression of atherosclerosis [20]. In diabetic disorder, high levels of TG, TC and low level of HDL including changed composition of LDL units were reported normally [21]. In the study, STZ presented changes of typical lipid profiles i.e. High TG, TC and LDL levels as well as low or reduced HDL level compared to control. These different lipid profiles were overturned to almost normal when treated with *Tamarixaphylla* and glibenclamide, respectively in STZ-treated diabetic rats. This lipid dropping action may be due to normalization of glucose level and increase in insulin level after administration of *Tamarixaphylla* which may normalize the troubled lipid breakdown in diabetic rats. Therefore, antihyperlipidemic result of *Tamarixaphylla* in diabetic rats claims its ability to avoid the CVD diseases allied with diabetes. The occurrence of phenolic compounds and tannins in *Tamarixaphylla* could be responsible for the antihyperlipidemic and hypoglycemic actions in diabetic rats.

Conclusion

Given study data settle that *Tamarixaphylla* possesses blood glucose dropping action in diabetic disorder. Furthermore, it has antihyperlipidemic in diabetes, so it has a capability to avoid diabetic problems. Therefore, above outcomes have set scientific confirmation to the traditional application of Tamarixaphylla leaves in the management of diabetes.

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