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EVALUATION OF ANTI- HYPERGLYCAEMIC ACTIVITY OF *MAYTENUS EMARGINATUS WILLD* LEAVES EXTRACT ON STREPTOZOTOCIN-INDUCED DIABETES IN WISTAR RATS

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ABSTRACT: *Maytenus emarginatus* Willd. Celeastraceae, popularly known as "Kankeri or kankero", is a Thorny staff evergreen tree that is rich in various chemical constituents that determine the medicinal potential of this species. Diabetes mellitus is a disease that is affecting major population of the world. This study aimed to evaluate the antihyperglycaemic activity of the hydroalcoholic extract of the leaves of *Maytenus emarginatus* plant which is widely found in dry and arid regions of India mainly in Rajasthan. The hydroalcholic extract of the leaves of *M. emarginata* (250 and 500 mg/kg/day) were administered orally to streptozotocin-induced diabetic rats (n = 6/group) for 21 days. Changes in body weight, food and water intake, biochemical markers, fasting glucose levels and oral glucose tolerance test were evaluated. The results showed that the *M. emarginatus* dried extract (250 and 500 mg/kg) reduced significantly the level of blood glucose comparable to glibenclamide (10mg/kg) throughout the evaluation period and improved metabolic status of the animals and ameliorate the oral tolerance glucose test. Thus, we conclude that the extract of the leaves of *M.emarginatus* has antihyperglycemic activity.

INTRODUCTION: Diabetes mellitus is a metabolic disorder characterized by increased levels of blood glucose, glycosuria, hyperkalemia and ketonemia [1] as a result of impaired insulin production, insulin resistance or both. It is associated to long-term damage of various organs such as eyes, liver, kidneys, nerves, blood vessels and it may cause degenerative diseases in central nervous system. [2] The prevalence of diabetes is projected to rise from 171 million in 2000 to 366 million in 2030. [3]

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Synthetic oral hypoglycaemic agents produce serious side effects so medicinal plants are screened for the potential antidiabetic agents [4] as plants are safer, cheaper and much effective [5] Plant compounds such as alkaloids, triterpenes, flavonoids, tannins, proteins, phenolics, lignans, flavonol [6] have been related to the betterment of hyperglycaemia in diabetes. *Maytenus emarginatus* Willd. is a traditionally valuable plant commonly known as kankero in hindi and " Thorny staff tree" in English. It belongs to the family Celeastraceae also known as bittersweet family.

It is an evergreen tree that tolerates various types of stresses of the desert and is found in dried and arid parts of central, south-western and north-western India. It provides fodder, timber and fuel. Besides this, it has also medicinal value. In Africa, the root

is used in gastro-intestinal troubles, especially to cure dysentery. Pulverized leaves are given in milk to children as a vermifuge. A decoction of the leafy twigs is used as a mouth wash to relieve toothache. The extract of plant shows cytotoxic effect on some cancers [7]. The plant is reported to possess antiplasmodic properties. Traditionally leaves are used in healing wounds, diabetes and jaundice treatment [8]. Fruits are used as a blood purifier [9]. Bark is grounded to a paste and applied with mustard oil to kill lice in head [10]. From the review of literature we came to know that no work till date was reported on the hypoglycaemic activity on this plant. Leaves are used to cure diabetes.[8] and the present study was designed to investigate the effects of prolonged treatment with hydroalcoholic extract of *M.emarginata* leaves on biochemical blood parameters, oral glucose tolerance test and other diabetic disorders of streptozotocin-diabetic rats

Experimental Section:

Collection of plant material:

The leaves of plant were collected from the desert field area in the month of August near Bikaner in Rajasthan and positively identified as *Maytenus emarginatus* (Family: Celastraceae) by Dr. H.B. Singh, Scientist Incharge, Raw Materials and Museum, National Institute of Science Communication And Information Resources, New Delhi where a voucher specimen (No.: NISCAIR/RHMD/consult/-2010-11/ 1549/147) has been deposited.

Preparation of Extracts:

Leaves of *M. emarginatus* were collected, washed, cleaned thoroughly so as to remove any type of contamination and dried in shade for two weeks. Dried leaves were coarsely powdered and stored in an air tight container at room temperature. Dried leaf powder was then extracted with hydroalcoholic solvent (70:30) using soxhlation method. The extract was concentrated to dryness using Rotary evaporator (Heidolph, model-4011, USA) and vacuum chamber.

Chemicals:

Streptozotocin was purchased from Sigma-Aldrich (St. Louis, USA). Chemicals were obtained from SD fine chemicals Ltd., Mumbai, India. All reagents and solvents used were of analytical grade. For estimation of blood glucose and other biochemical tests standard kits were obtained from Erba diagnostics Mannheim Gambh, Germany.

Animals:

Wistar rats (male) weighing about 200–250 gm were selected for experimental study. The animals were kept and maintained under laboratory conditions of temperature (21.5 ± 22°C), humidity (60 ± 1%), and 12-hour light/dark cycle. They were allowed for free access to food (standard pellets) and water *ad libitum*. Experimental protocols and procedures used in this study were approved by the Institutional Animal Ethics Committee (Ref. No. JNU/ IAEC/2015/1/7/A)

Acute toxicity:

As per OECD-423 guidelines, acute oral toxicity study was performed [11]. The extract was given to the animals (n=6) used for the study at increasing dose of 100, 250, 500 and 1000mg/kg for 28 days. The animals were observed continuously for various physical signs of toxicity and mortality. It was observed that at the dose of 500 mg/kg there was no mortality, so this dose is selected as safe dose.

Induction of diabetes:

After one week the rats were subjected to a 12-h fasting. The STZ was dissolved in freshly prepared citrate buffer (0.01 M, pH 4.5). Hyperglycaemia was induced by a single injection of streptozotocin (STZ) 60 mg/kg body weight intraperitonially. The blood glucose level was checked before and 72 h after streptozotocin injection to confirm the increase in blood sugar level. The diabetic animals were stabilized for five days and the experiment was started on the next day (day 0). Only those animals which showed increase in blood glucose levels >250 mg/dL were used in the study.

Experimental design:

Diabetic animals were randomly assigned into the following groups of six animals each and treated once a day for 21 days as follows.

Group I: normal control received 5 mL/kg of normal saline.

Group II: diabetic control received vehicle (Tween 80, 5% v/v and 5 mL/kg of normal saline).

Group III: diabetic rats received hydroalcoholic extract of *Maytenus emarginata* (250 mg/kg)

Group IV: diabetic rats received hydroalcoholic extract of *Maytenus emarginata* (500 mg/kg)

Group V: diabetic rats received Glibenclamide (10 mg/kg).

The drug solutions or vehicle were administered orally by gastric intubation once daily at 12 o'clock for 21 days. The effect of vehicle, extract, and standard drug on blood glucose and body weight was determined in animals.

Biochemical Parameters: Blood Glucose Was Measured With Elegance Glucometer (Frankenberg, Germany) At Weekly Intervals I.E. 0, 7, 14 And 21 Day After Daily Administration Of Extract Orally. After Blood Glucose Estimation On Day 21, Whole Blood Was Collected By Cardiac Puncture Under Mild Ether Anesthesia From Rats. Serum Cholesterol, Triglycerides, Creatinine, Urea, Alkaline Phosphatase, Hdl And Total Proteins Levels Were Also Evaluated In Normal And Streptozotocin Induced Diabetic Rats [12]. Serum Alanine Transaminase (Alt) And Serum Aspartate Transaminase (Ast) Were Measured By Autoanalyser (Erba Chem 7, Mannheim, Germany) Using Erba Diagnostic Kits [13]. Percentage Decrease In Blood Glucose Levels Of Extract Were Monitored At Various Time Intervals After Administration Of Extract At Both The Two Doses And Were Compared With Standard Treated Groups And Control Groups.

Statistical Analysis:

All values of results are presented as mean ± standard error of mean (SEM). The statistical analysis involving two groups was evaluated by means of Student's t test, whereas one way analysis of variance (ANOVA) followed by Dunnett's multiple comparison post test was used for statistical comparison between control and various treated groups. Statistical significance was accepted at the $P < 0.05$ values.

RESULTS: Single intra-peritoneal treatment of rats with Streptozotocin (60mg/kg) significantly ($p < 0.001$) increased the blood glucose level as shown in **Table 1**. The hyperglycemic effect of hydroalcoholic extract of *M. emarginatus* (HEME) at dose 250mg/kg and 500mg/kg was studied in diabetic rats. Continuation of treatment upto 21 days had shown significant ($p < 0.001$) lowering effect on blood glucose level as compared to the standard drug treated rats. Diabetes is also associated with altered lipid profile such as triglyceride (TG), total cholesterol (TC) and high density lipoprotein (HDL). There was significant increase of serum total cholesterol, TG and significant decrease in HDL cholesterol in diabetic rats as compared to that of normal control. The standard drug as well as treatment with HEME (250 and 500mg/kg) had significantly ($p<0.005$) reduced the level of TC and TG and increased the HDL cholesterol level after the 21 days treatment as shown in **Table 2**.

TABLE1: EFFECT OF HEME ON BLOOD GLUCOSE LEVEL IN STZ DIABETIC RATS.

Groups/Treatment	Blood glucose level (mg/dl)			
0 day	7 day	14 day	21 day	
I: Normal control	113.22 ± 2.5	113.35 ± 2.3	114.70 ± 3.22	114.93 ± 3.4
II:Diabetic control + vehicle	254.53 ± 2.45	297.56 ± 4.35	327.46 ± 4.27	391.24 ± 4.34
III: *M.emarginata* (250 mg/kg)	258.34 ± 2.43	233.26 ± 2.25*	186.53 ± 2.34*	127.23 ± 3.26*
IV: *M.emarginata* (500 mg/kg)	286.53 ± 2.5	203.23 ± 2.5*	141.22 ± 3.24*	117.58 ± 3.27**
V :Glibenclamide (10 mg/kg. b.w.)	254.24 ± 2.28	200.23 ± 3.52	129.31 ± 2.34*	114.42 ± 2.8

n=6, Data represent means ± S.E.M. *p<0.05, **p <0.001, When groups III, IV and V compared with diabetic control i.e. group II, n= Numbers of animals in each group

Effect of HEME on blood glucose level in STZ diabetic rats: Data are expressed as means ± S.D (n = 6). *p ≤ 0.05 compared with the corresponding value for vehicle control rats; ***p ≤ 0.001 compared with the corresponding value for vehicle control rats. ME250: *M.emarginata* (250 mg/kg);

ME500: *M.emarginata* (500 mg/kg); and it was compared with Glib10: Glibenclamide (10 mg/kg). From above study it can be revealed that in normal control the blood glucose level varies in very negligible rate with varies of number of days. Similarly, in case of diabetic control + vehicle, there was drastic change in the blood glucose level from 254.53±2.45 to 391.24 ± 4.34 (in 0 to 21 days). Where as in case of *M.emarginata* (250 mg/kg) & (500mg/kg), it showed decreased level of blood glucose level. Glibenclamide (10mg/kg) have least value of blood glucose level with the respect to days.

TABLE 2: EFFECT OF HEME ON LIPID PROFILE (mg/dl) IN STZ INDUCED DIABETIC RATS

Groups/Treatment	Total Cholesterol	Triglycerides	HDL cholesterol
I: Normal	86.27±3.7	82.41±5.15	37.32±2.8
II: Diabetic control	255±7.5	150±4.70	28.21±2.2
III:*M.emarginata* (250mg/kg)	123.45±2.23*	112.23±2.22*	34.24±2.23*
IV:*M.emarginata* (500mg/kg)	87.34±2.66*	82.66±3.22**	44.26±3.44*
V:Glibenclamide (10mg/kg b.w)	98.71±5.1*	83.41±4.4*	45.25±4.7**

Data represent means ± S.E.M. *p<0.05, **p <0.001, When groups III, IV and V compared with diabetic control i.e. group II, [a]p <0.05, When Group II compared with group I

Effect of HEME on lipid profile (mg/dl) in STZ induced diabetic rats:

Data are expressed as means ± S.D (n = 6). *p ≤ 0.05 compared with the corresponding value for vehicle control rats; ***p ≤ 0.001 compared with the corresponding value for vehicle control rats. ME250: *M.emarginata* (250 mg/kg); ME500: *M.emarginata* (500 mg/kg); and it was compared with Glib10: Glibenclamide (10 mg/kg). The total cholesterol of Normal control was found to be 86.27±3.7, triglyceride was found to be 82.41±5.15 & HDL cholesterol was 37.32±2.8. In case of diabetic control, total cholesterol was found to be 255±7.5.where as triglyceride was 150±4.70 & HDL cholesterol was 28.21±2.2. In case of *M.emarginata*, with change of concentration of dose, the level of cholesterol as well as triglyceride was lowered. In the similar manner in case of Glibenclamide it was found to be 98.71±5.1, 83.41±4.4, 45.25±4.7 respectively for total cholesterol, triglyceride and HDL cholesterol.

TABLE 3: EFFECT OF HEME ON LIVER PARAMETERS IN NORMAL AND DIABETIC RATS.

Groups	Total Protein (g/dL)	Bilirubin (mg/dL)	AST (U/L)	ALT (U/L)	ALP (U/L)
I: Normal control	7.25 ± 2.17	0.46 ±1.25	42.22 ± 2.24	59.36 ± 3.50	124.35 ± 3.33
II: Diabetic control + vehicle	5.27 ± 1.28	0.95 ±1.28 [a]	102.25 ± 4.86	114.23 ± 3.55	198.25 ± 4.38 [a]
III: *M.emarginatus* (250 mg/kg)	5.46 ± 3.47*	0.54 ± 1.27*	63.35 ± 3.42	61.32 ± 2.84*	143.53 ± 3.38*
IV: *M.emarginatus* (500 mg/kg)	8.34 ± 2.33**	0.45 ±1.39**	43.23 ± 3.16*	59.53 ± 4.32**	127.44 ± 1.85**
V :Glibenclamide (10 mg/kg. b.w.)	7.22 ± 1.25*	0.39 ± 1.83*	46.56 ± 3.54**	58.96 ± 3.58*	125.35 ± 3.25

Data represent means ± S.E.M., *p<0.05, *p<0.001, When groups III, IV and V compared with diabetic control i.e. group II, [a]p <0.05, When Group II compared with group I.

Effect of HEME on liver parameters in normal and diabetic rats:

Data are expressed as means ± S.D (n = 6). *p ≤ 0.05 compared with the corresponding value for vehicle control rats; ***p ≤ 0.001 compared with the corresponding value for vehicle control rats. ME250: *M.emarginata* (250 mg/kg); ME500: *M.emarginata* (500 mg/kg); and it was compared with Glib10: Glibenclamide (10 mg/kg). From above we can conclude that for normal control total protein there is no significant effect with respect to all.

Effect of HEME on kidney parameters in normal and diabetic rats:

Data are expressed as means ± S.D (n = 6). *p ≤ 0.05 compared with the corresponding value for vehicle control rats; ***p ≤ 0.001 compared with the corresponding value for vehicle control rats. ME250: *M.emarginata* (250 mg/kg); ME500:

M.emarginata (500 mg/kg); and it was compared with Glib10: Glibenclamide (10 mg/kg).

Effect on other biochemical parameters such as AST, ALT and ALP level was found to be increased in diabetic rat which was responsible for the hepatic damage. The animals treated with HEME showed significant ($p<0.001$) reduction in the elevated level of hepatic enzymes i.e. transaminase in a dose dependent manner. Bilirubin and total protein level was decreased significantly in diabetic rats after 21 days treatment while protein level was significantly increased ($p < 0.01$) as shown in **Table 3**. Kidney function markers like creatinine and urea were elevated in STZ induced diabetic rats as compared to the normal rats. HEME reduced the levels in dose dependent manner as shown in **Table 4**.

TABLE 4: EFFECT OF HEME ON KIDNEY PARAMETERS IN NORMAL AND DIABETIC RATS

Groups/Treatments	Serum Urea (mg / dl)	Serum Creatinine (mg/dl)
I: Normal	30.24 ± 1.57	0.64 ± 1.35
II: Diabetic control+ Vehicle	58.29 ± 1.58	0.96 ± 0.53 [a]
III: *M.emarginatus* (250 mg/kg)	37.56 ± 3.51	0.76 ± 2.33*
IV: *M.emarginatus* (500 mg/kg)	36.6 ± 1.35*	0.68 ± 3.75**
V: Std.Glibenclamide (10 mg/kg.b.w.)	35.36 ± 0.86*	0.65 ± 0.61**

Data represent means ± S.E.M., *p<0.05, *p<0.001, When groups III, IV and V compared with diabetic control i.e. group II, [a]p<0.05, When Group II compared with group I.

DISCUSSION: The present investigation reports the antidiabetogenic and hypoglycaemic property of chemical nature of the hydroalcoholic extract of plant. The antidiabetic and hypoglycaemic potential of this species of plant have action to potentiate of the insulin effect of plasma by increasing the pancreatic secretion of insulin from existing β cells of langerhans or its release. Considering the wide use of these plants in folk therapeutics for the treatment of diabetes, the present study was conducted to investigate the antihyperglycaemic activity of *M. emarginatus* in streptozotocin-induced diabetic rats. In this generation, herbal drugs are much more popular in treating the diabetes and its complications as it has more efficacy, low incidence of side effects and low cost [15]. This is the first study to show that the treatment with the hydroalcoholic extract of the leaves of *M. emarginatus* for 21 days exhibited significant antihyperglycaemic effect in streptozotocin-induced diabetic rats.

As a results of the acute toxicity test signify that HEME when administered orally at a dose of 5g/kg did not implies any sign of toxicity or death in the treated animals, suggesting an LD_{50} of above 5 g/kg. The phytochemical screening of this species has been shown to contain polyphenols, lignans and flavanol glycosides that have been considered to contribute to its antidiabetic properties [16]. In our study, the induction of diabetes was confirmed by high levels of fasting glucose, and as expected, the diabetic rats had polyphagia, polydipsia and polyuria. *M.emarginatus* induced a decrease in blood glucose that was similar to the standard anti-diabetic drug glibenclamide and this effect was also reflected by the decrease of daily water and food intake.

In general, the extract improved the metabolic status of animals in relation to the DC group. In diabetic rats, there was an increase in urea and uric acid levels in blood. The values of uric acid were diminished in the treated groups. Also there was a tendency to decrease (not significant) in the urea levels. The effect of HEME on the biochemical parameters and tissue mass were broads. In general, the extract improved the metabolic status of animals in relation to the DC group. In diabetic rats, there was an increase in urea and uric acid levels in blood. The values of uric acid were diminished in the treated groups. Also there was a tendency to decrease (not significant) in the urea levels. The treatment with HEME ameliorates these parameters. According to[17] during uncompensated diabetes, there is a decrease in body mass due to energy deficit and the cellular catabolic process characterized by glycogenolysis, lipolysis and proteolysis. In conclusion, our results show that the hydroalcoholic extract of the leaves of *Maytenus emarginatus* has antihyperglycaemic activity in streptozocin-induced diabetic rats. However, the

mechanism of action remains to be established. Some hypotheses include an antioxidant action, interference with insulin levels and the enzymatic pathways of protein kinase B and AMP-activated protein kinase.

In the present investigation, diabetes mellitus was induced in rats through a STZ injection that causes the destruction of b-cells of islets of Langerhans, as proposed by many authors [18]. This purport was represented in the current study by the rising of blood glucose and a decrease of insulin levels in diabetic control rats. The elevated plasma glucose levels in diabetic rats were lowered through the administration of HEME which showed raised plasma insulin level compared to diabetic control rats. The results of the present study showed an increase in skeletal muscle and liver glycogen content in diabetic rats after the oral administration of *M.emarginatus* which may be due to the stimulation of insulin release from beta cells [20]. Furthermore, the diabetic control rats showed a significant increase in the AUC of the glucose concentration after oral glucose loading. This effect may be due to the reduction of glucose tissue utilization and an increased hepatic glucose production, as a result of decreased insulin production [21].

The administration of *M. emarginatus* extract produced a significant reduction in the AUC of diabetic control rats. These results revealed that the *M. emarginatus* extract induced an increase in glucose utilization and glucose tolerance through the body tissues of diabetic rats. It is well known that dyslipidemia is associated with uncontrolled diabetes mellitus. It is known that the administration of insulin to diabetic subjects not only elevates lipoprotein lipase activity, but also lowers the plasma concentrations [22.] The presently observed decline in plasma lipid profiles in *M. emarginatus* administered diabetic rats suggests that the extract's potential is possibly due to the elevation of insulin level. The possible mechanism of the extract may in part be attributed to its antioxidant activities. Complementing our findings, earlier studies have reported that the extract may have antioxidant activity. A significant improvement in these indictors of oxidative stress in the liver of *M.emarginus* treated diabetic rats is indicative of its ability to reduce body glucose concentration, and its subsequent oxidation. These effects of *M.emarginatus* on antioxidants were found to be better than those of glibenclamide treated diabetic rats. In conclusion the *M.emarginatus* has both a hypoglycaemic effect and an antidyslipidemic activity. The possible mechanism of the antidiabetic action may be through a stimulation of insulin release from the remnant pancreatic β-cells. Both antidiabetic and antidyslipidemic effects may in part be due to its antioxidant activity.

CONCLUSION: These findings suggest that *Maytenus emarginatus* willd. has potent antidiabetic activity in streptozotocin induced diabetic rats.

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