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Study of hypoglycaemic and hypolipidemic activity of Eugenia Jambolana pulp and seed extract in Streptozotocin induced diabetic albino rats

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ABSTRACT

The aim of the present investigation was to evaluate the therapeutic efficacy of Eugenia Jambolana in an animal model of diabetes. Diabetes was induced in albino rats by administrating Streptozotocin 50mg/kg intraperitonial . Normal as well as diabetes albino rats were divided into groups (n=5) receiving different treatment: Control (vehicle) , diabetic (vehicle) ethanolic pulp extract (200mg/kg) ethanolic seed extract (200mg/kg) and standard antidiabetic drug glibenclamide (.6mg/kg b.w.) Blood samples collected from retro orbital sinus and estimated for blood sugar lipid profile, glycosylated haemoglobin blood urea on day 0, 7, 14 and 21. The effect on body weight was also observed. Blood glucose level, lipids and blood urea were elevated in diabetic group but were significantly brought down with treatment with seed and pulp extract. There was improvement in body weight with treatment. Eugenia Jambolana pulp and seed extract at a done of 200mg/kg body weight has therapeutic effect in diabetes induced albino rats. Therefore this investigation reaffirms the potential of EJ as natural oral agent as add on therapy to established oral hypoglycaemic agents and/or insulin. Further studies to isolate and characterize the active compound and to further elucidate the mechanism involved in the hypoglycaemic needs to be done.

Key word: Eugnia Jambolana **,** Diabetes Mellitus, Streptozotocin, Hypolipidemia and Hypoglycaemia

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INTRODUCTION

Diabetes mellitus is a chronic disease characterized by elevated blood glucose levels and disturbances in carbohydrate, fat and protein metabolism [1]. The world is facing an explosive increase in the incidence of diabetes mellitus which affects more than 100 million people worldwide [2] . The prevalence rate of diabetes is estimated to be 1-5% in India [3] . These metabolic abnormalities result in part from a deficiency of the blood sugar- lowering hormone insulin, this deficiency in insulin results in insulin dependent diabetes mellitus. (IDDM) . Non insulin dependent diabetes mellitus (NIDDM) is a result of hyperglycaemia caused by overproduction of glucose at the hepatic level or because of abnormal β cell function or insulin resistance at target cell [4]. The chronic hyperglycaemia of diabetes is associated with damage, dysfunction, and failure of various organs over the long term [5] . Abnormalities in lipid profile are one of the most common complication in diabetes mellitus which is found in more than 40% of diabetes [6] . The elevated lipids is significant risk factor for coronary heart disease [7]. Despite the availability of many antidiabetic medicines in the market, diabetes and its related complication continue to be major medical problems. Plant derivatives with purported hypoglycaemic properties are used in folk medicine and

traditional healing systems around the world [8] Because of their effectiveness minimal side effects and relatively low cost, herbal drug are prescribed widely even when their biologically active ingredients are unknown [9]. Substantial efforts have been made in recent years to identify new natural and synthetic antidiabeties. There is flood of scientific data about medicinal plants including those with antidiabetic potential [10] Eugenia Jambolana, popularly known as Jamun belonging to the family of myrtaceae has been indicated in ayurveda for use in diabetes mellitus [11] . As per claims of its anti-diabetic effects in traditional medicine Eugenia Jambolana has been reported to have hypoglycaemic effects both in pre clinical and clinical studies [12,13,14]. Eugenia Jambolana seed have been reported to have hypoglycaemic, hypolipidemic [15], anti-inflammatory [16], neuropsycho-pharmacological [17] anti ulcer [18], anti-bacterial [19], anti HIV [20] and antidiarrhoeal activity [21].

Although Eugenia Jambolana has been widely used in traditional medicine [15] yet scientific validation of the hypoglycaemic and hypolipidemic activity of pulp and seeds needs to be established . Hypoglycaemic activity of pulp extract is not well documented so its extract was further tested for action Hence this study was undertaken to evaluate the hypoglycaemic and hypolipidemic acitivity of Eugenia Jambolana in STZ induced diabetic rats. The result of the preclinical study could prove useful for clinical trials so that the side effects of drug induced hypoglycaemia may be minimised by the practice of integrated medicine [1].

Material and Method

Animals

Adults albino rats 25 in number weighing (150 g-200g) of either sexes were procured from small animal house of UFHT Medical College, Haldwani, Nainital Uttarakhand. They were kept in clear and dry plastic cages at 26± 2C and 45.55% relative humidity. The animals were fed with standard pellet diet and water was given ad libitum. For experimental purpose the animals were kept fasting overnight but allowed free access to water . Principles of laboratory animal care guidelines were followed and prior permission was sought from the institutional animal ethics committee for conducting the study.

Plant Material & Extract Preparation

Fruits of Eugenia Jambolana (EJ) was obtained from Udham Singh Nagar, Uttarakhand in the month of June-July. Fruit and seed were separated and each dried at room temperature and grounded in electric grinder to have course powder. Extraction of seed and pulp powder separately was done with adequate amount of 90% ethanol for 7 days and the extract so obtained was filtered . The procedure was again repeated twice using adequate amount of ethanol for 3 days . The extracts of pulp and seed was again filtered and mixed separately with previous lots. The yield of the ethanol extract was 13.5g/100g for seed and 11.5g/100ml for pulp. The antidiabetic drug glibenclamide .6mg/kg body weight taken as standard drug.

Induction of non-insulin dependent Diabetes mellitus (NIDDM)

NIDDM was induced in 20 rats by a single intraperitoneal injection of 50mg/kg streptozotocin (Sigma Aldrick, Germany) dissolved in freshly prepared 0.1M citrate buffer (PH 4.5) Control rats received citrate buffer only. Hyperglycaemia was confirmed by elevated glucose level in blood, determined at 72 hr. and then on day 7 after injection . The threshold value of fasting blood glucose to diagnose diabetes was taken as >126mg/dl . Those with fasting blood sugar level of 200-300 mg/dl and above were employed in the study [15].

Collection of blood and determination of blood glucose, Glycosylated Hemoglobin and blood urea

Blood samples were obtained from retroorbital sinus and glucose levels were estimated using glucose oxidase-peroxidase reactive strips and a glucometer. Fasting blood glucose was estimated at 0,7,14,21 and 30 days after streptozotocin injection.

Glycosylated haemoglobin was determined according to the ion exchange resin method .Blood urea was estimated by urea- glutamate dehydrogenase (GLDU) method.

Estimation of lipid profile

Total cholesterol estimation was done using the Erba diagnostic kit Serum triglyceride were estimated using Enzokit (Ranbaxy) .HDL cholesterol was determined using the Erba diagnostic kit. VLDLcholesterol was calculated as Triglyceride/5.

LDL cholesterol was calculated by the equation :

LDL cholesterol = Total cholesterol – (HDL + VLDL)

All estimation was done using Erba Transasia auto analyzer.

Experimental Design

Overnight fasted 25 rats were randomly divided for the antidiabetic study in the following manner.

Group I (control) and group II (diabetic control) received 1% carboxymethyl cellulose (CMC) in distilled water orally once daily.

Ethanolic seed and pulp extract of Eugenia Jambolana (EJ) suspended separately in 1% carboxymethyl cellulose (CMC) in distilled water (1ml/100g body weight) orally once daily in the doses of 100, 200, 400 mg/kg for 10 days for dose dependent effect in diabetic rats. An optimal dose of 200mg/kg of pulp and seed extract was then selected on the basis of our preliminary observation on the antihyperglycaemic activity of EJ.

Therefore Group III received ethanolic pulp extract of EJ suspended in 1% carboxymethyl cellulose in distilled water (1ml/100g body weight) was administered orally once daily in the dose of 200mg/kg from day 7 to day 30 after STZ injection.

Similarly Group IV received ethanolic seed extract of EJ orally once daily in the dose of 200mg/kg from day 7 to day 30 after STZ injection.

Group IV received standard antidiabetic drug glibenclamide .6mg/kg orally once daily [22,18].

The mean body weight, blood glucose, glycosylated haemoglobin, blood urea and lipid profile was estimated at 0,7,14,21 and 30 day of Streptozotocin injection.

Statistical Analysis

Statistical analysis was performed using Statistical Package for the Social Sciences (SPSS)software package. The values were analysed using one way Analysis of Variance (ANOVA), followed by Dunetts multiple comparison applied for comparing with the normal and diabetic control group.

The level of Significance was $p<0.05$

Result

Effect on body weight

STZ induced diabetic rats showed a significant decrease in body weight compared to normal rats from day 7 to 30 after STZ injection. Statistically significant increase in body weight was observed from days 21 to 30 with pulp and seed extract of EJ and glibenclamide.

Effect on blood glucose level and glycosylated hemoglobin

Control (Group I) rats did not show any significant variation in the blood glucose throughout the experimental period. Administration of STZ (group II) led to over 3.5 fold elevation of blood glucose levels which was maintained over a period of 4 weeks.

EJ pulp extract 200mg/kg/day(Group III) reduced the hyperglycaemia significantly as compared to the diabetic group II , it failed to restore the level to that of the control group . Same finding was seen with EJ pulp extract (group IV). **Fig.1.**

The rats on glibenclamide showed significantly reduced hyperglycaemia as compared to diabetic group II and restored blood glucose to near normal values.

Effect on Lipids Profile and blood urea table 3

Administration of vehicle to STZ induced diabetic rats resulted in significant increase in the level of TG, TCH, LDL, VLDL ,blood urea and decrease HDL. Continuous administration of ethanolic seed and pulp extract led to a significant fall in the level of TG, TCH, LDL, VLDL and blood urea and improved the HDL level. Glibenclamide also showed significant reduction in the levels of TG, TCH, LDL, VLDL and blood urea and improved HDL .

Table 3 also shows the changes in glycosylated hemoglobin level after 4 weeks. The ethanolic seed and pulp extract of EJ had significant effect in lowering it in the diabetic rats (Group III and IV).

Discussion

Diabetes Mellitus is a chronic disorder caused by partial or complete insulin deficiency, which produces in adequate glucose control and leads to acute and chronic complications . Premature and extensive arterio-sclerosis involving renal, peripheral and cardiovascular vessels remain the major complication of Diabetes Mellitus. Alteration in the serum lipid profile is known to occur in diabetes and this is likely to increase the risk of coronary heart disease. A reduction in serum lipids, particularly of the LDL and VLDL fraction and triglyceride, should be considered as being beneficial for the long term prognosis of these patients. Lowering of blood glucose and plasma lipid levels through dietary modification and drug therapy seems to be associated with a decrease in the risk of vascular disease .

Streptozotocin is believed to partially destroy the pancreatic β-cell of islet of langerhans of the pancreas[23] . Induction of diabetes with STZ in this study is associated with characteristic loss of body weight which is due to increased muscle wasting and loss of tissue protein . Treatment with seed and pulp extract of EJ caused significant gain in weight which is in accordance with the reports of other researchers. [24] The hypoglycaemic influence of EJ seed extract concurs with the observation made by other researchers studying EJ [1,15,,18] . The hypoglycaemic activity was compared with glibenclamide a sulphonylurea glibenclamide stimulate insulin secretion from pancreatic β cell [23] . Thus hypoglycaemic effect of EJ may be due to increased secretion of insulin from the β cell

of the pancreas i.e. pancreatrotrophic action or inhibition of insulin degradation [24]. Active principles present in plants have been demonstrated these effects [24] for example benzoic acid related molecules and adhepsin β which inhibit insulinase and enhance insulin effect [25,26,27,28] .Pytochemical and pharmacological studies , indicated that ethanol extract contain flavonoids, saponins and traces of phenol and steroid . Saponin appear to be involved in stimulation of pancreatic β-cells and subsequent secretion of insulin[27].

Glycohaemoglobin is formed through the circulatory life of RBC by the addition of glucose to the N-terminal of the haemoglobin beta chain. This process, which is non-enzymatic reflects the overall exposure of haemoglobin to glucose over extended period.

Several investigators have recommended that glycosylated haemoglobin be used as an indicator of metabolic control of diabetes since glycohemoglobin level approach normal values in diabetes in metabolic control. In the present study it was elevated nearly 2.5 times above normal in the diabetic group. In the group (III, IV, V) with seed and pulp extract of EJ and glibenclamide respectively, levels of glycosylated haemoglobin approached the normal value as also seen is various other studies [1].

The most common lipid abnormality in diabetes are hypertriglyceridemia and hypercholesterolemia [29] which is risk factor for atherosclerotic coronary heart disease [7]. The abnormal high concentration of serum lipids in the diabetic patient is due to increase mobilization of free fatty acid from the peripheral fat depots, since insulin inhibit hormone sensitive lipase . Acute insulin deficiency causes increase in free fatly acid mobilization from adipose tissue [15]. Repeated administration of EJ for 4 weeks significantly lowed TG, TCH, LDL, VLDL and improved HDL level which was also seen in various other studies [15] [30] .

Elevated levels of urea occurs in diabetes mellitus due to increased protein down and may also be seen in renal disorders like glomerular nephritis and chronic nephritis. In the present investigation elevated level of blood urea in the diabetic group were restored to near normal level. To the best of our knowledge the effect of EJ on blood urea have not been studied by other workers .EJ did not exhibit any sign of toxicity.

Conclusion

The use of cost- effective therapies is very essential to control the rising incidence of Diabetes Mellitus in developing countries . The aqueous seed and pulp extract of Eugenia Jambolana has antidiabetic, antihyperlipidaemic activity and lowers blood urea in diabetic rats. It also increases body weight of diabetic rats. Therefore this investigation reaffirms the potential of EJ as natural oral agent as add on therapy to established oral hypoglycaemic agents and/or insulin. Further studies to isolate and characterize the active compound and to further elucidate the mechanism involved in the hypoglycaemic needs to be done.

Table 1 : Effect of Eugenia Jambolana pulp and seed powder on body weight of STZ diabetic rats .

Group	Days of STZ injection (days of treatment)				
	0 day	7days (0days)	14 days (7 days)	21days (14 days)	30days (21 days)
I normal Control	187 ± 4	170 ± 4	193 ± 3	194 ± 3	197 ± 3
II Diabetic Control	181 ± 7	154 ± 5*	147 ± 7*	142 ± 8*	138 ± 7*
III Diabetic + pulp 200mg/kg	182 ± 10	165 ± 10	168 ± 8	169 ± 6#	171 ± 10#
IV Diabetic + seed 200mg/kg	182 ± 5	164 ± 2	168 ± 3	169 ± 4#	171 ± 4#
V Diabetic + glubenclamide .6mg/kg	188 ± 5	162 ± 5	169 ± 4	171 ±4#	177 ± 4#

Data are reported as means ± SEM for groups of 5 animals each.

* p <0.05 compared to normal control

\# p <0.05 compared to diabetic control

Table 2 : Effect on Eugenia Jambolana pulp and seed extract on blood glucose level mg/dl in normal and STZ injected rats .

Group	Blood glucose level after days of STZ (days of treatment)				
	O day (no treatment)	7days (0days)	14days (7 days)	21days (14 days)	30days (21 days)
I normal Control	68.9 ± 1.2	69.5 ± 2.7	70.4 ± 4.8	71.2 ± 3.7	69.5 ± 3.0
II Diabetic Control	70.2 ± 1.8	253.2 ± 2.1*	251.2± 6.1*	252.2 ± 7.2*	250.3± 6.1*
III Diabetic + pulp 200mg/kg	66.1 ± 1.6	246.1 ± 2.6	242.3 ± 3.8	178.3 ± 6.8#	136.2 ± 4.8 #
IV Diabetic + seed 200mg/kg	67.2 ± 1.2	247.3 ± 3.1	235.3 ± 2.8	166.2 ± 8.2#	135.2 ± 3.2#
V Diabetic + glubenclamide . 6mg/kg	70.1 ± 1.3	245.2 ± 2.6	200.2 ± 2.2#	135.3 ± 5.8#	80.3 ± 4.8#

Data are reported as means ± SEM for groups of 5 animals each.

* p <0.05 compared to normal control

\# p <0.05 compared to diabetic control

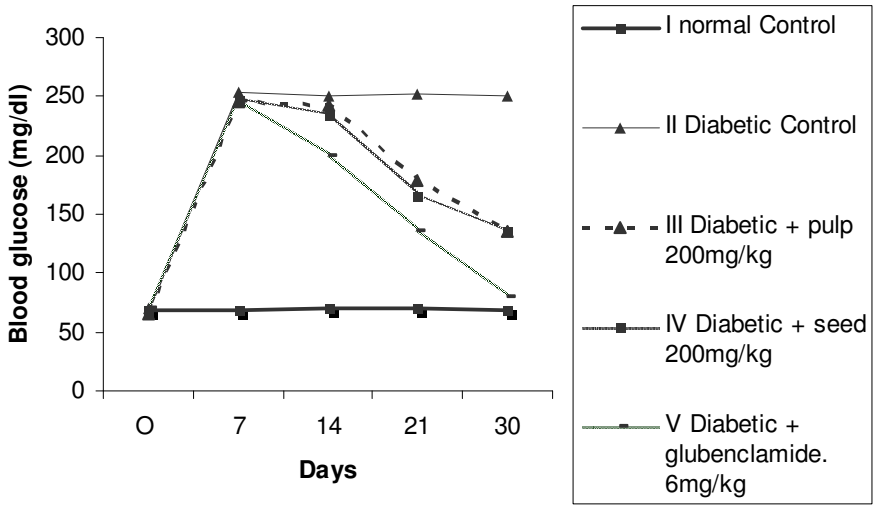

Fig. 1. Effect on Eugenia Jambolana pulp and seed extract on blood glucose level mg/dl in normal and STZ injected rats .

Table 3 : Effect on EJ pulp and seed extract on lipid profile mg/dl and blood urea mg/dl in normal and STZ injected rats.

Lipid Profile	Period	Group				
		I normal Control	II Diabetic Control	III Diabetic + pulp 200mg/kg	IV Diabetic + seed200mg/kg	V Diabetic + glubenclamide . 6mg/kg
TG (mg/dl)	0 day	80.11 ± 1.52	79.11 ± 1.47	81.11 ± 1.32	80.19 ± 1.42	82.18 ± 1.30
	30 days	80.61 ± 1.94	138.94 ± 2.42*	99.12 ± 2.78 #	98.16 ± 2.66*	101.63 ± 3.52#
TCH (mg/dl)	0 day	76.41 ± 1.35	75.48± 1.23	76.98 ± 1.33	74.38 ± 1.34	77.31 ± 1.00
	30 days	76.45 ± 0.90	131.45 ± 2.90*	90.46 ± 1.80#	91.41 ± 1.70#	93.08 ± 2.32#
HDL (mg/dl)	0 day	22.16 ± 1.31	24.18 ± 2.13	23.18 ± 1.84	20.32 ± 1.36	21.32 ± 1.62
	30 days	22.16 ± 1.36	15.36 ± 1.57*	16.06 ± 1.81	16.08 ± 1.80	21.16 ± 1.22#
LDL (mg/dl)	0 day	38.26 ± 1.31	35.48 ± 1.36	37.6 ± 1.78	38.07 ± 2.84	40.73 ± 1.12
	30 days	38.17 ± 1.50	88.30 ± 2.81*	51.88 ± 2.23 #	53.20 ± 1.10#	51.60 ± 2.17 #

VLDL(mg/dl)	0 day 30 days	16.10 ± 1.47 16.12 ± 1.60	15.82 ± 1.39 27.79 ± 2.41*	16.22 ± 1.32 19.82 ± 0.71 #	16.20 ± 1.45 19.63 ± 0.76 #	16.42 ± 1.45 20.32 ± 1.28 #
Glycosylated Hb(%)	0 day 30 days	5.36 ± 0.18 5.34 ± 0.18	5.93 ± 1.21 11.46 ± .49*	6.12 ± 1.34 6.7 ± 0.74 #	6.01 ± 1.32 6.60 ± 0.71 #	5.76 ± 1.82 6.24 ± 0.17#
Blood urea (mg/dl)	0day 30 days	37.12 ± 1.48 37.16 ± 2.10	36.16 ± 1.32 77.61 ± 2.22*	36.98 ± 1.48 48.2 ± 2.06 #	36.53 ± 1.53 47.9 ± 2.01 #	37.01 ± 1.83 42.24 ± 1.68 #

Data are reported as means ± SEM for groups of 5 animals each.

* $p < 0.05$ compared to normal control

\# $p < 0.05$ compared to diabetic control

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