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EVALUATION OF HYPOGLYCEMIC AND HYPOLIPIDEMIC ACTIVITIES OF *ZIZYPHUS JUJUBA*

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Abstract:

Objective: *The present study was designed to evaluate the hypoglycemic and hypolipidemic activity of methanolic extract of zizyphus jujuba leaves in normal and streptozotocin inducing diabetic rats. Zizyphus jujuba Lam. is also called as Baer tree, belongs to the family Rhamnaceae. It is used primarily for its fruits. Jujube, a delicious fruit, is an effective herbal remedy improving stamina and muscular strength and aids weight gain, strengthens liver function and increases immune system resistance.*

Methods: *The dried bark was powdered and extracted with various solvents by successive soxhlet hot extraction process with increasing order of polarity. On phytochemical investigation, the methanol extract and aqueous extract has shown steroids, flavonoids and tannins. The zizyphus jujuba was reported for the many of biological activity, and hypoglycaemic activity of the same has not been reported so far. Streptozotocin is used to induce diabetic in rats and the blood lipid levels were estimated using commercial kits available in the market. The methanolic extract of Zizyphus jujuba was administered at the doses 100mg/kg and 200mg/kg.*

Results : *The methanolic extracts of Zizyphus jujuba 100mg/kg and 200mg/kg produced significant decreased $p<0.01$) in blood glucose level after 2,4 and 6 hour of treatment as compared to untreated diabetic rats respectively as 503±3.6, 163±3.9 (67±6.1) ,128±10.7 (74±2.2) ,125±5.4 (74±1.0) , 511±4.2, 262±4.5 (55±6.7), 205±2.8 (59±5.7) , 208±2.3 (58±4.8).*

The treatment of diabetic rats with (Group III) extracts for 3 weeks resulted in significant decrease of serum triglycerides, total cholesterol and LDL-c cholesterols as compared to untreated diabetic rats (Group II) and the values came down significantly ($p<0.01$) below those in the normal healthy control group .

Conclusion: *The results indicate that methanolic extract of Zizyphus jujuba in the dose dependent manner possess hypoglycaemic and hypolipidemic activity.*

Keywords: *Zizyphus jujuba, Diabetic rats, Streptozotocin, hypoglycemic, hypolipidemic*

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INTRODUCTION:

Diabetes mellitus is a term employed to describe a metabolic disorder characterized by persistent hyperglycaemia with disturbances of carbohydrate, fat, and protein metabolism resulting from defects in insulin secretion, insulin action, or both [1].The long-term effects of diabetes mellitus include progressive development on the specific complications of retinopathy, nephropathy, and/or neuropathy [2] People with diabetes are at increased risk of cardiovascular disease [3]. Diabetes affects a large proportion of Mexican adults (8.18%), it is the most common cause of death in Mexico [4] and it has been estimated that close to 11.7 million Mexicans will have diabetes by the year 2025 [5]. The use of herbal medicines for the treatment of diabetes mellitus has gained importance throughout the world and there is an increased demand to use natural products with antidiabetic activity due to the side effects associated with the use of insulin and oral hypoglycemic agents [6].

Hyperlipidemia causes about 17 million deaths worldwide each year [7] in addition, it is also a key factor for the development of heart and coronary diseases and atherosclerosis. Atherosclerosis is a chronic inflammatory disease triggered by multiple factors, with strong contribution of endothelial damage related to lipid peroxidation. This endothelial dysfunction increases the permeation of low-density lipoproteins (LDL) through the intima layer, resulting in oxidation and formation of atherosclerotic damage [8,9]. In order to control this imbalance, the body has enzymatic and nonenzymatic antioxidant defense mechanism [10] capable of preventing the deleterious effects of oxidation, inhibiting lipid peroxidation, free radicals scavenging, and maintaining redox balance in cells. In addition to endogenous antioxidants, there are antioxidants from exogenous sources. The beneficial effects of foods have been linked to the presence of bioactive compounds and other nutrients. Examples of biomolecules that have antioxidant potential are phenolic compounds such as isoflavones, phenolic acids, catechins, chlorogenic acids, anthocyanins, and terpenes [11]. Thus, plants have been described as an alternative to the development of new drugs [12] applied to treatment of many diseases such as hypercholesterolemia, ulcers, depurative blood, and cancer [13-15].

Zizyphus jujuba Lamk is also called as Badar, Baer, Bogari, Barihannu belonging to family Rhamnaceae. The plant is distributed throughout India, Iran, Afghanistan and in china. It is a small sub deciduous tree with dense spreading crown, commonly 0.6m girth and 6m high. Leaves 3-6.3 by 2.5-5 cm oblong or ovate, usually minutely serrulate or apex distinctly toothed, obtuse, base oblique and 3-nerved, nerves depressed on the glabrous shining upper surface, densely clothed beneath with white or buff tomentum [16,17]. A survey of literature on *Zizyphus jujuba* lam. revealed a few pharmacological reports on the plant like antioxidant and anti-listerial effect [18] anti-steroidogenic activity [19] anti-obesity activity [20] sedative and hypnotic [21] anxiolytic[22] anticancer [23]. The plant is reported to contain alkaloid jubanine-E[24]. It contains three flavones-Cglucosides-6"sinapoylspinosin, 6"-feruloylspinisin and 6-"p-coumaroylspinosin. The leaves and stems of *ziziyphus jujuba* lam contains saponins 3-o-[2-α-L-fucopyrnosyl-3-o-β-Dglucopyranosyl-α-L-arabinopyranosyl] jujubogenin. The fruits of Zizyphus jujuba lamk contain zizyphus saponins I, II, III and jujuboside B [25] jujuboside D [26] and jujuboside e [27]. The bark of zizyphus jujuba Lamk contains 7% tannin [28].

MATERIALS AND METHODS:

Plant material *Ziziphus jujuba* leaves were collected from in and around chembarambakkam, Chennai, India and authenticated by Dr.P.Jayraman, Director of Plant Anatomy Research Centre, Chennai. The fresh leaf of *Ziziphus jujuba* was identified and deposited at Department of Pharmacognosy, Sree Sastha Pharmacy College, Chembarambakkam, Chennai with the voucher number SSCPDPCOG/03/2020. The fresh leaf was separated and kept for shade drying. Dried leaf material was powdered using a mechanical grinder and passed through 60 mesh sieves to get the powder of desired coarseness. Powdered material was preserved in an airtight container.

Extraction of Plant material

The leaves of *Z.jujuba* were washed thoroughly in water to remove foreign matter and allowed to shade dry with a relative humidity of 40–45%. Then, leaves were powdered in roller grinder and passed through a sieve (No. 60). Then, the fine powder (Approx. 150 gm) was defatted with petroleum ether and extracted with water and 1 litre of Methanol at room temperature by using Soxhlet apparatus for 72 hours. The resultant extract was filtered and concentrated in a rotary evaporator under reduced pressure to obtain a brownish black colour residue. was stored at −20°C until required. The yield of the extract was found to be 7.2 %w/w. The methanol extract was collected and used for the present study.

Animals

Albino wistar rats of either sex weighing between 150-250 gm maintained in the Animal house facility of the Department of Pharmacology, Sree Sastha Pharmacy College were used in these experiments. The animals were maintained on standard small animal feeds (Excel feed, Ilorin) and water ad libitum. The study protocol was approved by the Institutional Animal Ethics Committee (IAEC)

under the reference no. 1332/DPCG//20 /CPCSEA and CPCSEA guidelines adhered to during the maintenance and experiment. This research was carried out in accordance with the rules governing the use of laboratory animals as accepted internationally. The experiment was conducted between the hours of 900 h and 1600 h. The experimental groups consisted of six animals. They were maintained at constant room temperature (22° ± 1 °C) and submitted to12 h light/dark cycle with free access to food and water.

EXPERIMENTAL PROCEDURE:

Acute oral toxicity study

Acute oral toxicity was conducted as per OECD guidelines (Organisation of Economic Cooperation and Development) 423 (Acute toxic class method). The acute toxic class method is a stepwise procedure of three animal of a single-sex per step. Depending on the mortality and/or moribund status of animals, on the average 2-4 steps may be necessary to allow judgment on the acute toxicity of the test substance. This procedure results in the use of a minimal number of animals while allowing for the acceptable data-based scientific conclusion. The method uses defined doses, (5, 50, 300, 2000 mg/kg body weight) and the results allow a substance to be ranked and classified according to the globally harmonized system (GHS) for the classification of chemicals which causes acute toxicity. The method previously described by Lorke was adopted [29].

Hypoglycaemic activity& Hypolipemic activity

Albino wistar rats of either sex weighing between (150-200gms) were divided into five groups of six animals in group. Twenty-four rats fasted for 18hr, were made hyperglycaemic by intraperitoneal injection to streptozotocin (sigma) dissolved in citrate buffer (pH-4.5), at a dose of 60mg/kg body weight. After 72hr of STZ injection, the rats were fasted for 6hr and their plasma glucose levels estimated. Rats having plasma glucose levels above. 250mg/dl14 were considered diabetic. The 24 diabetic rats were randomly divided into following 5 groups of 6 each [30-35]

Group I Control group (Healthy control) -Injected with equal volume of 10% physiological saline
Group II: Diabetic rats maintained on unrestricted standard diet and water ad libitum and served as untreated diabetic rats.
Group III: Diabetic rats treated orally with Methanolic extract of *Ziziphus jujuba* (100mg/kg b.w)
Group IV: Diabetic rats treated orally with Methanolic extract of *Ziziphus jujuba* (200mg/kg b.w)
Group V: Diabetic rats received orally glibenclamide (10mg/kg b.w).

Treatments for 21 days in all groups were started 4 days after STZ injection. The bodyweight of the animals was recorded after the termination of the experiment. Blood samples were collected from overnight fasted animals at 0,2,4,6 hr and 21 days after treatment. Whole blood was used for the estimation of haemoglobin and glycosylated haemoglobin (Hg A1C). Hb and glycosylated haemoglobin (Hb A1c) blood glucose, serum triglyceride (TAG) total cholesterol and high-density lipoprotein cholesterol (HDL-c) were estimated.

Low density lipoprotein cholesterol (LDL-c) was estimated by the equation of Fried Ewald et al
LDL-c = TC-HDL-c-TAG/5

Statistical analysis: -

The results were expressed as mean ± SEM, (n=6). Statistical analysis was performed with one-way analysis of variance (ANOVA) followed by Dennett's' test P value less than <0.01 was considered to be statistically significant when compared with healthy control

RESULTS:

Table-1: Anti-diabetic activity of methanolic extract of *Z.Jujuba* in Streptozotocin induced hyperglycaemic rats

Treatment and Dose	Serum Glucose level mg/dl time after treatment			
	0	2	4	6
Group-I Normal control	90±4.8	95±3.5	93±1.8	97±2
Group-II Diabetics	500±4	505±3.0	500±4	503±3.5
Group-III MEZJ 100mg/kg	503±3.6	163±3.9** (67± 6.1)	128±10.7** (74±2.2)	125±5.4** (74±1.0)
Group-IV MEZJ 200mg/kg	511±4.2	262±4.5* (55±6.7)	205±2.8* (59±5.7)	208±2.3 * (58±4.8)
Group-V STD Glibenclamide 10mg/kg	510±3.9	388±3.9 * (22.6±0.9)	345±6.0 * (31.2±0.85)	348±6.0 * (31.8±0.8)

Values are the mean ± S.E.M. of 6 rats / treatment
Significant *P < 0.01 and **P < 0.001 compared with Control.
MEZJ-Methanolic extract of *Ziziphus jujuba*

Fig1-Anti-diabetic activity of methanolic extract of *Z.Jujuba*

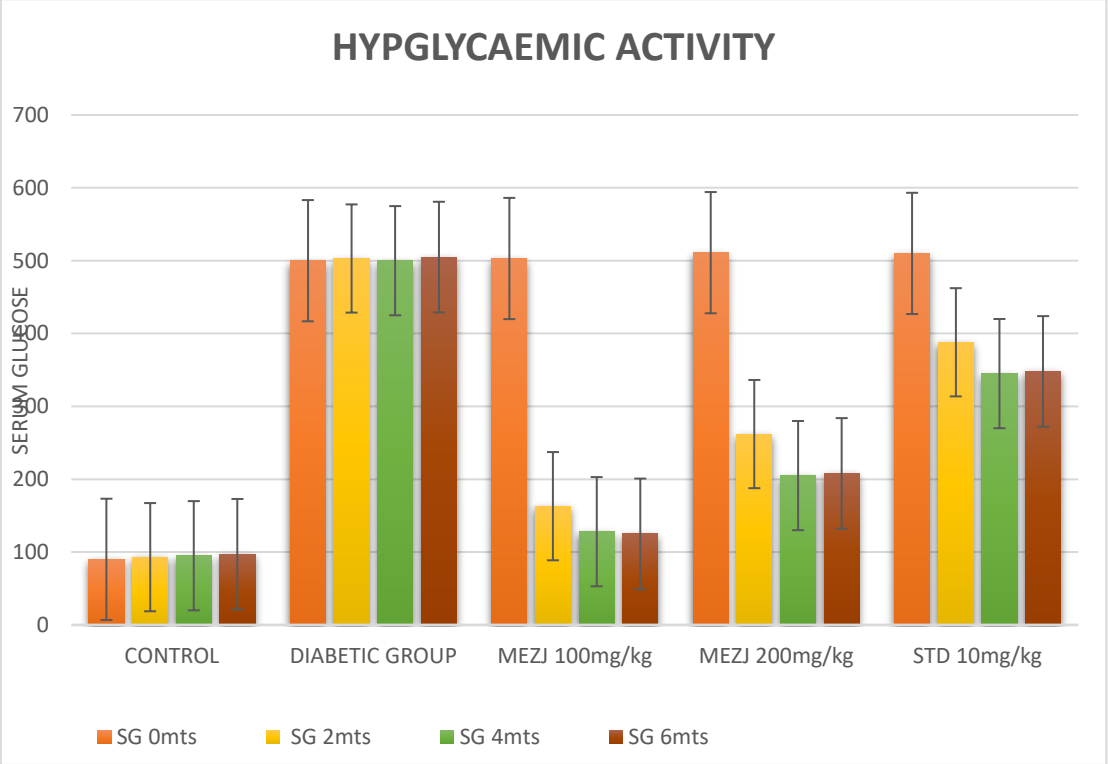
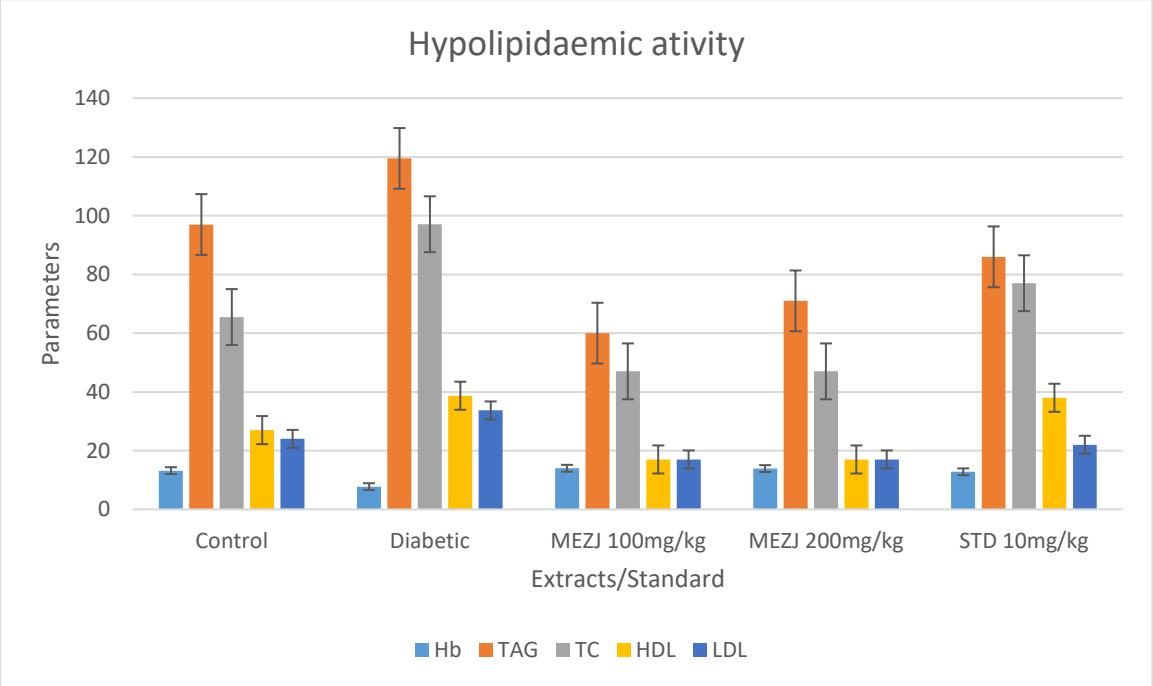


Table: 2 various biochemical parameters of serum and fasting glucose, lipid profile, blood haemoglobin and glycosylated in streptozotocin-induced hyperglycaemic rats before and 3-weeks after treatment with Zizyphus jujuba extract

Treatment and Dose	Hb (g/dL	Hb1Ac Mg/g Hb	Glucose (mg/dl)	TAG (mg/dl)	TC (mg/dl)	HDL-c (mg/dl)	LDL-c (mg/dl
Group-I Normal control	13.2±0.4	0.35±0.02	90±4.8	97±5.4	65.5±3	27±2.7	24±0.48
Group-II Diabetics	7.75±0.4	0.97±0.4	505±3.5	119.5±6.4	97.1±4.1	38.7±1.9	33.7±3.1
Group-III MEZJ 100mg/kg	14±0.3	0.3±0.02	72±4.4 (84±0.7)	60±3.2* (51±1.4)	47±3 * (53±2.8)	17±1.1* (57±3.0)	17±3.3* (67±4.4)
Group-IV MEZJ 200mg/kg	13.9±0.3	0.32±0.03	82±4.1$ (83±0.9)	71±9 (36±2.9)	47±3* (53±2.8)	17±1.1* (57±3.0)	17±3.3* (67±4.4
Group-V STD Glibenclamide 10mg/kg	12.8±0.5	0.35±0.02	76±0.3 (84±0.1)	86±1.1 (26±609)	77±3.2 (27±5.4)	38±0.726	22±2.5 (18±0.9)

Values are the mean ± S.E.M. of 6 rats / treatment, Significant *P < 0.01 compared with Control. MPZJ-Methanolic extract of *Ziziphus jujuba*
Hb=Haemoglobin, HbA1C=glycosylated haemoglobin, TAG=triglycerides, TC=total cholesterol, HDL-c=High density lipoprotein cholesterol LDL-c=Low density cholesterol.

Fig -2: various biochemical parameters of serum and fasting glucose, lipid profile, blood haemoglobin and glycosylated in streptozotocin-induced hyperglycaemic rats before and 3-weeks after treatment with Zizyphus jujuba extract



MPZJ-Methanolic extract of *Ziziphus jujuba*
Hb=Haemoglobin, TAG=triglycerides, TC=total cholesterol, HDL-c=High density lipoprotein cholesterol LDL-c=Low density cholesterol.

The methanolic extracts of *Zizyphus jujuba* 100mg/kg and 200mg/kg produced significant decreased p<0.01) in blood glucose level after 2,4 and 6 hour of treatment as compared to untreated diabetic rats respectively as 503±3.6, 163±3.9 (67±6.1) ,128±10.7 (74±2.2) ,125±5.4 (74±1.0) , 511±4.2, 262±4.5 (55±6.7), 205±2.8 (59±5.7) , 208±2.3 (58±4.8).

The treatment of diabetic rats with (Group III) extracts for 3 weeks resulted in significant decrease of serum triglycerides, total cholesterol and LDL-c cholesterols as compared to untreated diabetic rats (Group II) and the values came down significantly (p<0.01) below those in the normal healthy control group.

A significant decrease in body weight was observed in the untreated diabetic group (Group-II: 200±6.6g) as compared to the control group. (Group-I: 200±6.1g). The administration of the extracts resulted in a significant decrease in body weight (190±5g) (180±2g) respectively.

DISCUSSION:

The results of blood glucose showed that rats of group II-V, injected with streptozotocin developed severe diabetes with very much higher initial blood glucose level of about 500511mg/dl when compared to the blood glucose of healthy. (Group-I) control group (90±4.8) feeding diabetic rats with 100mg/kg, 200mg/kg body wt of methanolic extracts of Zizyphus jujuba produced significant decreased in blood glucose level after 2,4 and 6 hours of treatment as compared to untreated diabetic rats. Glibenclamide also showed similar results (84% reduction). Hb and HbA1c level-there was a significant decrease in Hb level in untreated diabetic rats (Group I) as compared to control rats (Group I). After treatment with both the extracts (Group III and IV) and Glibenclamide (Group V), the levels of HbA1c returned to the normal values. Serum lipid profile- the results of the serum lipid profile (Table 2) showed that in Streptozotocin induced diabetic rats (Group II) there was not only hyperglycaemia but also hyperlipidaemia in which serum triglycerides, total cholesterol, HDL-c, and LDL-c cholesterols increases significantly when compared to control group (Group I). The treatment of diabetic rats with (Group III) extracts for 3 weeks resulted in significant decrease of serum triglycerides, total cholesterol and LDL-c cholesterols as compared to untreated diabetic rats (Group II) and the values came down significantly below those in the normal healthy control group (Group I).

CONCLUSION:

In conclusion MEZJ was shown to have dose dependent glucose lowering and antihyperlipidemic effects. As per the above parameters observed MEZJ showed significant antidiabetic and anti-hyperlipidaemic effects of STZ induced diabetes. Further studies deal with the isolation of active constituents from MEZJ and their mechanism for the antidiabetic and antihyperlipidemic activity.

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Competing interests:

Author have declared that no competing interests exist.

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