

***In vivo* antidiabetic potential of *Artocarpus heterophyllus* plant seeds in streptozotocin-induced-diabetic rats**

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ABSTRACT

Artocarpus heterophyllus is a medicinal plant, used by herbalist for treating various diseases, one of which is *Diabetes mellitus*. The aim of this study was to investigate the antidiabetic potential of *Artocarpus heterophyllus* plant seed powder. This was tested in normal and streptozotocin induced diabetic rats using oral administration of ethanol extracts of *Artocarpus heterophyllus*. After the oral administration of ethanol extract at doses of 400 mg/kg body weight, blood glucose levels were monitored at specific intervals and found significantly lowered the blood glucose level. Glibenclamide was used as a standard drug at a dose of 0.25 mg/kg. The experimental data revealed that extract has significant antihyperglycaemic activity in streptozotocin-induced rats compared to standard drug. The extracts seem promising for the development of an oral antidiabetic medicine.

Key words: Antidiabetic, Lipid profile, *Artocarpus heterophyllus*, Streptozotocin, Glibenclamide

INTRODUCTION

Every year the number of diabetic patients is growing alarmingly all over the World. Diabetes is a chronic disease characterized by derangement in carbohydrate, fat, protein metabolism. Most of the hypoglycemic agents used in allopathic medicines are reported to have side effects in the long run. Therefore, there is a need to search for effective and safe drugs for diabetes.

The jackfruit (*Artocarpus heterophyllus*) is a species of tree in the mulberry family (Moraceae), which is native to parts of South and Southeast Asia. It is called *Katahal* in Hindi, medium-size evergreen tree typically reaching 8–25 m (26–82 ft) in height that is easily recognized by its fruit. Its fruit is the largest tree borne fruit in the world,

seldom less than about 25 cm in diameter. The jackfruit is something of an acquired taste, but it is very popular in many parts of the world. Seeds are light brown to brown, rounded, 2–3 cm in length by 1–1.5 cm in diameter, and enclosed in a thin, whitish membrane and has a sweet taste. Up to 500 seeds can be found in each fruit. The nutritious seeds are boiled or roasted and eaten like chestnuts, added to flour for baking, or cooked in dishes (1-4). The main objectives of this study was to assess the antidiabetic potential of ethanol extracts of powdered seeds of *Artocarpus heterophyllus* in control of blood glucose levels and effectiveness on various biochemical parameters viz total cholesterol, triglycerides (TGL), high density lipoprotein, (HDL), low density lipoprotein, (LDL), very low density lipoprotein, (VLDL).

MATERIAL AND METHODS

Plant material

The fruit seeds *Artocarpus heterophyllus* has been collected from Hyderabad district of Andhra Pradesh, India. The species for the proposed study was identified as *Artocarpus heterophyllus* by Dr. P. Jayaraman, Botanist, Plant Anatomy Research Centre (PARC), Chennai.

Preparation of *Artocarpus heterophyllus* seeds ethanolic extract

The powder of seeds (300gm) of *Artocarpus heterophyllus*, was packed well in Soxhlet apparatus and extracted with ethanol until the completion of the extraction. The extract was filtered while hot, and the resultant extract was distilled in vacuum under reduced pressure in order to remove the solvent completely and dried in a desiccator⁵.

Animals

Male wistar albino rats having weight 170-220gm were kept in quarantine for 10 days under standard husbandry conditions (27.3°, Relative humidity 65 ±10%) for 12 hrs in dark and light cycle respectively and were given standard food and water *ad libitum*. The study was permitted by the Institution Animal Ethical Committee.

Acute toxicity testing

Acute toxicity testing was performed for ethanol extract following OECD guidelines-420, fixed dose Procedure. Where a fixed dose level of extract starting from 50, 100, 200, 500, 1000, increasing upto 2000mg/kg body weight was given, sign and symptoms of toxicity were observed for next 48 hrs. No toxicity or death was observed in experimental rats (6, 7).

Oral glucose tolerance test (OGTT)

The oral glucose tolerance test⁸ was performed in overnight fasted (18 h) normal rats. Rats divided into two groups ($n = 6$) were administered drinking water, *Artocarpus heterophyllus* ethanol extract (400 mg/kg), respectively. Glucose (2 g/kg) was fed 30 min prior to the administration of extracts. Blood was withdrawn from the retro orbital sinus at 30, 60 and 120 min of extract administration and the plasma

obtained after centrifugation at 3000 rpm was estimated for fasting plasma glucose levels using a glucose oxidase–peroxidase glucose estimation kit.

Induction of non-insulin dependent diabetes mellitus (NIDDM)

NIDDM was induced^{9,10} in overnight fasted adult Wistar strain albino male rats weighing 170–220 gm by a single intraperitoneal injection of 60 mg/kg streptozotocin, 15 min after the i.p. administration of 120 mg/kg of nicotinamide. Streptozotocin (STZ) was dissolved in citrate buffer (pH 4.5) and nicotinamide was dissolved in normal saline. Hyperglycemia was confirmed by the elevated glucose levels in plasma, determined at 72 h and then on day 7 after injection. The threshold value of fasting plasma glucose to diagnose diabetes was taken as > 126 mg/dl. Only those rats were found to have permanent NIDDM were used for the study.

EXPERIMENTAL

The animals were segregated into four groups of six rats each. The extract was administered for 12 days. Group I served as normal control rats administered drinking water daily for 12 days; Group II diabetic control rats administered drinking water daily for 12 days; Group III diabetic rats administered ethanol extract (400 mg/kg); Group V diabetic rats administered standard drug Glibenclamide (0.25 mg/kg) for 12 days. The fasting glucose levels were determined on day 1, 5 and 12 of extract administration.

Estimation of biochemical parameters

The biochemical parameters were determined on day 12 after the animals were sacrificed by cervical dislocation. Total cholesterol, triglycerides (TGL), high-density lipoprotein (HDL), low-density lipoprotein (LDL), very low-density lipoprotein (VLDL), by Glucose oxidase method using auto-analyzer (11, 12).

Histopathology

All the animals were sacrificed on 12th day by cervical dislocation, pancreas were isolated and were subjected to histopathological studies and microscopical findings were noted.

Statistical Analysis

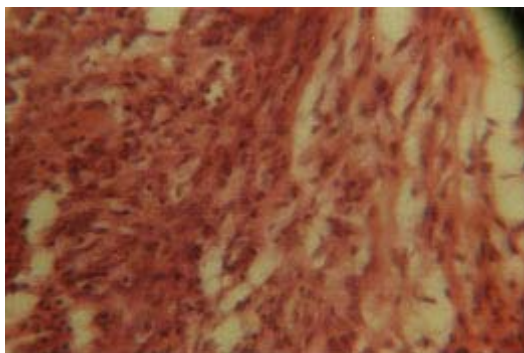
The results are expressed as mean \pm SEM of six independent experiments. Statistical significance between group was evaluated by one-way analysis of variance (ANOVA) followed by Tukey's multiple comparison test. A $P < 0.05$ value was considered as statistically significant.

RESULTS AND DISCUSSION

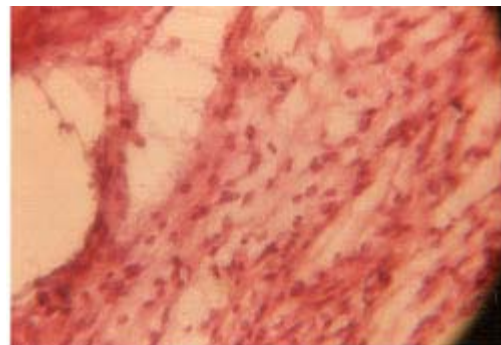
In our study, the difference observed between the initial and final fasting plasma glucose levels of different groups under investigation revealed a significant elevation in blood glucose in diabetic control group as compared with normal animals at the end of the 12-day experimental period. When ethanol extract of *Artocarpus heterophyllus* was administered to glucose loaded normal rats fasted for 18 h, significant decrease in plasma glucose level was observed after 30 min. The extracts reduced plasma glucose level to normal at 90 min (Table 1). During study it was found that

extract control significantly the blood glucose level on streptozotocin induced diabetic rats. The ethanol extract induced a significant reduction on blood glucose level in STZ-induced-diabetic rats as compared to the diabetic control group (Table 2). But ethanol extract showed significant antidiabetic activity as compared to standard drug. The possible mechanism by which *Artocarpus heterophyllus* brings about its hypoglycemic action in diabetic rat may be by potentiating the insulin effect of plasma by increasing either the pancreatic secretion of insulin from the existing beta cells or by its release from the bound form.

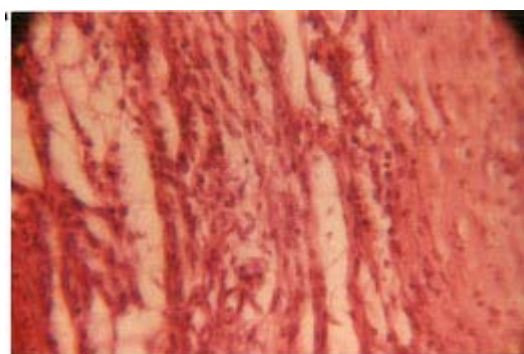
Abnormalities in lipoproteins are very common in both NIDDM and IDDM. Although lipoprotein alterations appear to be an intrinsic part of these disorders, such alterations are also induced by diabetes associated complications such as obesity and renal disease (13). The total cholesterol, triglyceride levels, VLDL and LDL were observed to be elevated in diabetics but reduced by extract



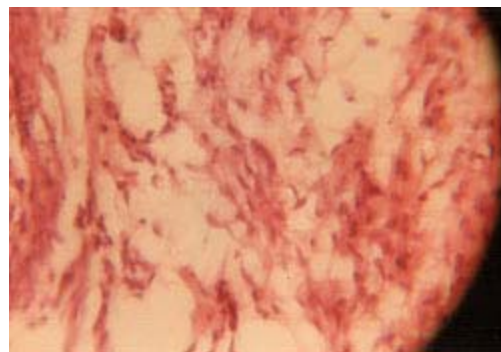
(a) Normal Pancreas



(b) STZ induced beta cell degeneration



(c) Ethanol extracts treatment - 400 mg/kg



(d) Glibenclamide 0.25 mg/kg

significantly as well as glibenclamide showing their beneficial effects. In the present study, HDL levels remained unchanged in diabetics compared to the other groups (Table 3). These results suggest the beneficial effects of the natural extract in improving the imbalance in lipoprotein metabolism are also comparable to those of glibenclamide.

The histopathological study of normal group (Fig. 1a) showed a normal pancreatic structure. The pancreas presents in the group of animals treated with ethanol extract (Fig. 1c) showed more or less similar appearance of pancreatic lobules, acing and cells as compared to standard drugs (Fig. 1d), whereas pancreas of diabetic

Table 1: Effect of ethanol extract of *Artocarpus heterophyllus* on oral glucose tolerance test

Group	Plasma glucose concentration (mg/dl)		
	30 min	60 min	90 min
Normal control	72.55±1.94	97.79±2.07	95.49±2.17
Normal + Ethanol Extract	66.76±1.76	83.88±2.33*	72.87±1.27*

Values are expressed as mean ± SEM (Number of animals, n=6); * Significantly different from the normal control at P<0.05

Table 2: Effect of ethanol extract of *Artocarpus heterophyllus* on fasting plasma glucose level in rats

Group	Fasting plasma glucose concentration (mg/dl)		
	Day 1	Day 5	Day 12
Normal control	82.21±1.43	84.87±1.87	81.48±1.83
Diabetic control (Streptozotocin)	199.4±1.62*	212±2.29*	236.6±2.79*
Diabetic + Ethanol Extract(400 mg/kg)	196.6±1.86*	122.6±2.91*	94.15±2.85*
Diabetic + Standard Glibenclamide (0.25 mg/kg)	200±2.69*	102.9±2.29*	80.90±1.83

Values are expressed as mean ± SEM (Number of animals, n=6); * Significantly different from the normal control at P<0.05

Table 3: Determination of biochemical parameters after treatment with ethanol extract of *Artocarpus heterophyllus* and Glibenclamide

Group	Total cholesterol (mg/dl)	HDL (mg/dl)	Triglycerides (mg/dl)	VLDL	LDL
Normal control	84.20±3.01	54.41±2.69	85.35±2.91	34.4±2.69	43.56±3.64
Diabetic control (Streptozotocin)	154.43±4.04*	51.13±1.97	182.5±3.08*	68.7±3.51*	160.3±4.43*
Diabetic + Ethanol Extract(400 mg/kg)	74.8±2.84	46.87±3.34	103.5±3.46*	25.02±3.45	82.84±2.99*
Diabetic + Standard Glibenclamide (0.25 mg/kg)	60.75±4.32*	48.6±3.15	90.99±4.52	31.54±1.92	38.52±2.42

Values are expressed as mean ± SEM (Number of animals, n=6); * Significantly different from the normal control at P<0.05

control animals showed partially damaged or even destroyed pancreatic lobules, acing, cells, islet size, shaped and number (Fig. 1b).

Ethanol extract (400mg/kg) showed significant antidiabetic activity when compared with

standard drug (Glibenclamide 2.5 mg/kg). Present work have indicated the fact that the plant *Artocarpus heterophyllus*, has antidiabetic constituents and production of a safe antidiabetic drug is very much possible from the seeds.

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