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Antidiabetic and Antihyperlipidemic Activity of *Cucurbita maxima* Duchense (Pumpkin) Seeds on Streptozotocin Induced Diabetic Rats

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The objective of the present study was to evaluate the antidiabetic and antihyperlipidemic effect of petroleum ether, ethyl acetate and alcohol extract of seeds *of Cucurbita maxima* for its purported use in diabetes. The antidiabetic and antihyperlipidemic activity of different extracts of *Cucurbita maxima* seeds was evaluated in wistar albino rats against streptozotocin (50 mg/kg i.p.) at dose of 200 mg/kg p.o. for 21 days. Glibenclamide (500µg/kg) was used as reference drug. Fasting blood glucose (FBG) levels were measured on day 0, 7, 14 and 21. It was found that blood glucose concentration was significantly ($P<0.05$) decreased compared to control. In addition, oral administration of *Cucurbita maxima* significantly ($P<0.05$) decreased serum total cholesterol, LDL, VLDL, triglycerides and at the same time markedly increased serum insulin and HDL-cholesterol levels. Administration of glibenclamide, a reference drug also produced a significant ($P<0.05$) reduction in blood glucose concentration in streptozotocin-induced diabetic rats. Thus, the results of this experimental study shows that *Cucurbita maxima* possess antidiabetic and antihyperlipidemic effect and is able to ameliorate the diabetic state and is a source of potent antidiabetic agent

Keyword: *Cucurbita maxima*, Glibenclamide, Streptozotocin, Antidiabetic Activity, Antihyperlipidemic Activity.

1. Introduction

Diabetes mellitus, a complex syndrome is characterized by the imbalance in blood glucose homeostasis leading to hyperglycemia (high blood glucose) and a series of secondary complications caused by an absolute or relative lack of insulin. Abnormalities in lipid profile are one of the most common complications in diabetes mellitus, which is found in about 40% of diabetes[1]. Diabetes induction causes increase in cholesterol, triglycerides, LDL and VLDL[2]. The levels of serum lipids is usually elevated in diabetes mellitus and such an elevation represents the risk factor for coronary heart disease[3]. Besides drugs classically used for the treatment of diabetes (insulin, sulfonylureas, biguanides and thiazolidinediones) several species of plants have been described in the scientific and popular literature as having a hypoglycemic activity[4]. Because of their perceived effectiveness, minimal side effects in clinical experience and relatively low costs, herbal drugs are prescribed widely even when their biologically active compounds are unknown[5]. The present study investigate the effect of oral administration of petroleum ether, ethyl acetate and alcoholic extract of *Cucurbita maxima* on blood glucose and lipid profile in diabetic rats.

The pumpkin, *Cucurbita maxima* Duchense belongs to family cucurbutaceae. It is a trailing annual herb with somewhat prickly or hairy stem and axillary tendrils, leaves simple, alternate; flowers large, yellow, unisexual, solitary; fruits fleshy, round or oval, brown; seeds ovoid or oblong, compressed[6,7] . *Cucurbita maxima* is widely cultivated throughout India and in most warm regions of the world, for use as vegetable as well as medicine. Both of its fruits and the aerial parts are commonly consumed as vegetable. This plant has been traditionally used in many countries such as India, China, Brazil, Yougoslavia and America as antidiabetic, antitumor, antihypertensive, anti-inflammatory, immuno-modulatory and antibacterial agents[6,8,9,10,11,12,13]. Popularity of pumpkin in various traditional system of medicine for several ailments focused the investigator's attention on this plant.

A daily supplement of pumpkin in fruit powder was found to reduce blood glucose levels significantly ($P<0.05$) in the 20 NIDDM diabetics[14]. Although yet more scientific validation of the hypoglycemic and hypolipidemic activity of the seeds needs to be established. Therefore, the present study was undertaken to evaluate the antidiabetic and antihyperlipidemic activity of seeds of *Cucurbita maxima* in streptozotocin-induced diabetic rats.

2. Material and Methods

2.1 Plant Material

The plant used in this study, *Cucurbita maxima* seeds were collected from local market of Jaipur and were identified and authentificated by the Department of Botany, University of Rajasthan, Jaipur (Rajasthan), India. A voucher specimen (No. RUBL-20941) were kept in the herbarium department for future reference.

2.2 Preparation of Extract

The seeds were cleaned well with water and dried in a shadow place. After complete drying, the seeds were powdered and were extracted by using soxhlet apparatus with petroleum ether, ethyl acetate and alcohol as solvents for extraction. Solvents elimination under reduced pressure afford a solid residue (% yield). The yield of petroleum ether, ethyl acetate and alcohol are 7.80%, 8.62% and 9.84% respectively. The dry residue of the crude extract obtained were stored at 4^0C for further use.

The pumpkin extracts were analyzed for the presence of phytochemicals[15,16]. The phytochemical screening gave positive tests for carbohydrates, flavonoids, tannins, phenolic and saponins.

2.3 Experimental Animals

Healthy wistar albino rats of either sex weighing 150-170g were used for this study. Before starting the experiment, the animals were acclimatized to the laboratory conditions for a period of 2 weeks at an ambient temperature (24±2 ºC) and relative humidity (40-60%). The light - dark cycle was followed. The animals were fed with standard laboratory diet and water *ad libitum*. The animals were fasted for overnight before the study but had free approach to water. All the experimental procedure and protocols were reviewed and approved by the Institutional Animal Ethical Committee (IAEC) and all the experiments were carried out by following the guidelines of CPCSEA.

2.4 Drug Administration

Various extracts (Petroleum ether, Ethyl acetate, Alcohol) of *Cucurbita maxima* was suspended in distilled water and administered orally through ingastric tube at dose of 200 mg/kg body weight. The administration of the herbal extracts and standard drugs were carried out every day for 21 days. Blood samples were collected through the tail vein just prior to and on days 0,7,14 and 21 after the drug administration.

2.5 Acute Oral Toxicity Study

The rats were treated with graded dose of powered seed extracts of *Cucurbita maxima* (5, 50, 300, 2000 mg/kg body wt./rats/day) to find out any possible toxic effects and/or changes in behavioral pattern, and were kept under close

observation. All symptoms including changes in awareness, mood, motor activity, posture activity & mortality were recorded and no changes were observed in behavior and mortality as well as in toxicity or death for these given dose levels in the selected and treated animals. The LD_{50} of the pet ether, ethyl acetate and alcoholic extracts was found more than 2000 mg/kg whereas as per OECD guidelines-423 it is 2000 mg/kg so it was prove that extracts were not having any toxic effects. One-tenth of the maximum safe dose of the extract tested for acute toxicity were selected for the experiment. Hence, On the basis of above observations the biological dose was fixed 200 mg/kg Body weight for each the extracts for further treatment[17,18].

3. Biochemical Analysis
3. Antidiabetic Activity
3.1 Experimental Design

Evaluation of antidiabetic effect of test plant extracts was done on six groups of rats by randomly selecting six rats for each group. The groups are as following.

3.2 Induction of Diabetes in Rats

Rats were made diabetic by single administration of streptozotocin (50 mg/kg) dissolved in 0.1M citrate buffer, pH 4.5 was intraperitoneal injected to overnight fasted rats. The blood samples were collected from tail vein using capillary tubes. The blood glucose level was measured and the rats were having blood glucose level more than 200 mg/dl were considered as diabetic and used for the study[19,20,21].

3.3 Recording of Body Weight

The change body weight was recorded during the study period. Body weight was measured before and after the streptozotocin administration on the 0, 7^{th}, 14^{th} and 21^{st} study days during the treatment in normal control, diabetic control, standard glibenclamide, petroleum ether, ethyl acetate and alcoholic extracts[22].

Table 1: Grouping of animals [19,20,21]

Group No.	Description
1	Served as normal control (Received normal saline 0.5 ml/kg body weight).
2	Served as diabetic control (treated with STZ dissolved in 0.1M sodium citrate buffer pH 4.5 at a dose of 50 mg/kg body weight).
3	Served as reference standards (glibenclamide, 500 µg/kg body weight orally).
4	Diabetic rats given pet ether extract of *Cucurbita maxima*, 200 mg/kg body weight which is prepared in 1 % CMC and was given orally.
5	Diabetic rats given ethyl acetate extract of *Cucurbita maxima*, 200 mg/kg body weight which is prepared in 1 % CMC and was given orally.
6	Diabetic rats given alcoholic extract of *Cucurbita maxima*, 200 mg/kg body weight which is prepared in 1 % CMC was given orally.

3.4 Collection of Blood Sample

Blood samples for estimation of blood glucose was collected from each animal from the tip of the tail under mild ether as an anesthesia on 0^{th} day (before treatment) and 7^{th}, 14^{th}, 21^{st} days (during treatment). The blood samples for measuring lipids profile, liver functions tests were collected on 21^{st} day from each animal by retro-orbital route in Eppendroff's test tubes and serum was separated by centrifuge at 3000 rpm[20,21].

3.5 Estimation of Blood Glucose Level

Blood sugar estimation was done by using a glucometer (Accu-check® sensor, Roche Diagnostics GmbH, Mannheim) and strips. Blood glucose level was measured on the 0^{th}, 7^{th}, 14^{th} and 21^{st} study days during the treatment in normal control, diabetic mice standard glibenclamide, pet ether, alcoholic and aqueous extracts[23,24].

3.5. Estimation of Lipid Profile

Lipid profile (Total cholesterol, Triglyceride, LDL, HDL and VLDL) were estimated by using Star 21 bio auto analyzer (E114947) at 505 nm by standard kits (Span diagnostics Ltd. India).

3.6. Estimation of Liver Physiological Profile

Liver function parameters (ALP, SGOT, SGPT & Total bilirubin) estimations were carried out by Star 21 bio auto analyzer (E114947), using standard kits (Span diagnostics Ltd. India)

3.7 Statistical Analysis

The results were expressed as mean ± SEM; n=6 animals in each group; * P<0.05: Statistically significant from diabetic control; Statistical analysis was carried out using Graph Pad PRISM software (version 4.03). One way ANOVA was used, followed by Bonferroni multiple comparison tests; Diabetic control was compared with control rats. Diabetic + Glibenclamide, diabetic + Pet ether extract, diabetic + Ethyl acetate extract and diabetic + alcoholic extract were compared with diabetic control.

4. Results

The results of body weight, blood glucose level, lipid profile and liver function parameters of normal control group, diabetic control group, standard group (Glibenclamide 500 µg/kg) and three different extracts (Petroleum ether, Ethyl acetate and Alcohol) of herbal drug *Cucurbita maxima* were summarized in table no.1,2,3,4.

4.1 Effect of extracts on body weight

Table-1 shows that a significant decrease was observed in the body weight of diabetic rats compared with control rats. Treatment with extracts of seeds of *Cucurbita maxima* and glibenclamide, the body weight gain was improved but the effect was more pronounced in alcoholic extracts of *Cucurbita maxima* treated rats than glibenclamide on 14, 21st day of study.

Table-1: Effect of *Cucurbita maxima* extracts on body weight recorded before & after streptozotocin administration

Groups	Before STZ	Body weight after streptozotocin (gm)			
		0th	7th	14th	21st
Control	161.2±5.963	160.1±5.833	160.8±5.961	161.7±6.382	162.4±7.729
Diabetic control	164.3±7.657	164.2±7.158*	162.8±6.725*	160.8±5.725*	158.4±5.329*
GLB	153.9±7.232	153.2±7.441*	154.6±6.146*	155.2±5.689*	156.8±5.146*
Pet. ether extract	159.2±7.696	158.5±8.369*	159.1±8.382*	160.2±8.462*	161.6±7.314*
Eth. acetae extract	158.8±8.221	157.7±8.408*	158.6±8.284*	159.3±7.343*	160.8±7.145*
Alcoholic extract	160.5±7.146	159.6±8.375*	160.9±7.354*	161.7±7.151*	163.2±7.014*

The results are expressed as mean ± SEM; n=6 animals in each group; Values are statistically significant at *P<0.05; Statistical analysis was carried out using Graph Pad PRISM software (version 4.03). One way ANOVA was used, followed by Bonferroni multiple comparison tests; GLB = Glibenclamide

4.2 Estimation of blood glucose level

Table-2 shows that treatment with oral glibenclamide & various extracts of seeds of *Cucurbita maxima* diminished blood glucose level on day 0, 7th, 14th & 21. The untreated diabetic control rat group showed increase in blood glucose level throughout the entire study period. Initially blood glucose level of untreated diabetic control group was 288.6±2.376 and after 21 days of trial period the blood glucose level was increased to 318.6±4.471. For trial drugs *Cucurbita maxima* (200 mg/kg) blood glucose were studied in three different groups of animals. All the three groups showed a significant decrease of blood glucose level on streptozotocin-induced diabetic rats when compared to control group. The initial readings of blood glucose level of Petroleum ether, Ethyl acetate and Alcoholic

extract were 289.7±3.375, 287.5±3.402 and 285.3±3.753 respectively. After the trial period, there was marked reduction in blood glucose levels 264.1±1.815, 230.8±2.712 and 189.9±1.896 in 21 days. However alcoholic extract of *Cucurbita maxima* has shown maximum effect than petroleum ether and ethyl acetate. In standard group initial blood glucose was 270.6±1.783 and the post test was 141.6±1.113 which showed that the standard drug produced maximum hypoglycemic effect and the statistical analysis was extremely significant and slightly higher than that of trial drug group.

Table-2: Effect of *Cucurbita maxima* on blood glucose level

Groups	Blood glucose (mg/dl)			
	0 day	7th day	14th day	21th day
Control	86.2±1.713	86.5±1.317	86.8±1.610	86.5±0.992
Diabetic control	288.6±2.376	292.7±4.502	301.8±3.120	318.6±4.471
Glibenclamide	270.6±1.783*	168.3±1.332*	152.8 ±1.878*	141.6±1.113*
Pet. ether extract	289.7±3.375*	281.3±2.232*	272.4±1.793*	264.1±1.815*
Eth.acetate extract	287.5±3.402*	263.4±2.282*	242.3±2.343*	230.8±2.712*
Alcoholic extract	285.3±3.753*	230.5±2.354*	209.7±1.835*	189.9±1.896*

The results were expressed as mean ± SEM; n=6 animals in each group; * P<0.05: Statistically significant from diabetic control; Statistical analysis was carried out using Graph Pad PRISM software (version 4.03). One way ANOVA was used, followed by Bonferroni multiple comparison tests; Diabetic control was compared with control rats. Diabetic + Glibenclamide, diabetic + Pet ether, diabetic + Ethyl acetate extract and diabetic + alcoholic extract were compared with diabetic control.

4.3 Estimation of Lipid Profile of *Cucurbita maxima*

Table-3 shows the levels of Total Cholesterol (TC), Triglycerides (TG's), Low Density Lipids (LDL), High Density Lipids (HDL) and Very Low Density Lipids (VLDL) levels in liver of control and experimental rats. The results showed that increased levels of TC, TG's, LDL and VLDL in diabetic rats when compared with normal rats. In rats treated with different extracts of *Cucurbita maxima* and Glibenclamide there was a significant decrease in content of TC, TG's, LDL and VLDL levels and significantly increase in HDL levels when compared with diabetic control rats.

4.4 Estimation of Liver Physiological Profile of *Cucurbita maxima*

Table-4 shows the levels of ALP, SGOT, SGPT and Bilirubin in liver of control and experimental rats. The results showed that increased levels of ALP, SGOT, SGPT and Bilirubin in diabetic rats when compared with normal rats. In rats treated with different extracts of *Cucurbita maxima* and Glibenclamide there was a significant decrease in content of ALP, SGOT, SGPT and Bilirubin levels when compared with diabetic control rats.

Table-3: Effect of extract of seeds of *Cucurbita maxima* on lipid profile

Drug	Total cholesterol (mg/dl)	TG (mg/dl)	LDL (mg/dl)	HDL (mg/dl)	VLDL (mg/dl)
Control	94.79±1.376	62.72±1.011	47.62±1.182	38.66±0.874	11.48±0.672
Diabetic Control	145.03±1.979	93.25±2.191	82.47±1.252	23.72±1.439	19.47±0.479
GLB	98.21±1.928*	65.91±1.285*	42.31±1.505*	39.13±0.871*	12.24±0.187*
PE	131.27±2.738	88.16±1.983*	69.77±1.186*	24.55±2.681	23.37±1.232*
EAE	125.13±1.732*	81.26±1.872*	66.89±1.831*	32.46±1.667*	19.24±1.341*
AE	111.47±1.765*	77.13±1.516*	57.46±0.987*	29.88±0.816*	17.28±1.211*

The results were expressed as mean ± SEM; n=6 animals in each group; * P<0.05: Statistically significant from diabetic control;Statistical analysis was carried out using Graph Pad PRISM software (version 4.03). One way ANOVA was used, followed by Bonferroni multiple comparison tests; GLB = Glibenclamide; PE=Pet. ether extract; EAE=Ethyl acetate extract; AE= Alcoholic extract.

Table-4: Effect of *Cucurbita maxima* on liver function parameters

Groups	ALP (IU/L)	SGOT (IU/L)	SGPT (IU/L)	Bilirubin (IU/L)
Control	156.08±3.532	65.6±2.356	51.52±2.651	0.72±0.011
Diabetic control	267.81±3.114	125.51±1.744	105.41±2.312	2.12±0.094
Glibenclamide	172.18±2.063*	58.32±1.511*	63.20±2.451*	0.65±0.515*
Pet. ether extract	242.84±1.934*	116.52±1.662*	93.56±2.843*	2.11±1.015*
Eth. acetate extract	217.32±1.707*	102.18±1.432*	84.28±1.856*	1.81±0.842*
Alcoholic extract	204.28±1.662*	94.24±1.464*	72.08±1.498*	1.57±0.040*

The results were expressed as mean ± SEM; n=6 animals in each group; * P<0.05:Statistically significant from diabetic control; Statistical analysis was carried out using Graph Pad PRISM software (version 4.03); One way ANOVA was used, followed by Bonferroni multiple comparison tests.

5. Discussion

Diabetes mellitus is one of the most common chronic disease and is associated with hyperglcaemia, hyperlipidemia and co-morbidites such as obesity, hypertension. Hyperlipidemia is a metabolic complication of both clinical and experimental diabetes. Streptozotocin, an analogue (2-deoxy-2-(3-methyl-3-nitrosouredia)-D-glucopyranose), is a potent diabetogenic agent and widely used for inducing diabetes in a variety of animals by the selective degeneration and necrosis of pancreatic cells[26,27]. Streptozotocin selectively destroys pancreatic insulin secreting β-cells causing diabetes close to type-2 diabetes of humans[28]. Streptozotocin induces a wide variety of animals species by damaging the insulin secreting pancreatic β-cells, resulting in a disease in endogenous insulin release, which

paves the ways for the decreased utilization of glucose by the tissues+. Glibenclamide has been used for many years to treat diabetes to stimulate insulin secretion from pancreatic β-cells[30]. The present data indicated that different extracts of *Cucurbita maxima* significantly reduced the elevated fasting blood glucose with respect to those of diabetic control animals. The maximum result obtained from alcoholic extract of *Cucurbita maxima.* The possible mechanism by which *Cucurbita maxima* brings about its hypoglycemic action may be potentiating the insulin effect of plasma by increasing either the pancreatic secretion of insulin from β-cells of islets of langerhans or its release from bound insulin or increased peripheral utilization of glucose.

Lipids play a vital role in the pathogenesis of diabetes mellitus. The level of serum lipids is usually elevated in diabetes mellitus and such an elevation represents the risk factor coronary heart disease[3]. High levels of total cholesterol and more importantly LDL-cholesterol in blood are major coronary risk factor[31,32]. The abnormal high concentration of serum lipids in the diabetic subjects is due, mainly to the increase in the mobilization of free fatty acids from the peripheral fat depots, since insulin inhibits the hormone sensitive lipase. Acute insulin deficiency initially causes an increase in free fatty acid mobilization from adipose tissue. The most common lipid abnormalities in diabetes are hypertriglyceridemia and hypercholesterolemia[33,34]. Significant lowering of total cholesterol and rise HDL-cholesterol is a very desirable biochemical state for prevention of atherosclerosis and ischaemic conditions[35]. The various extracts (petroleum ether, ethyl acetate and alcohol) of *Cucurbita maxima* brought down the elevated levels of TC, LDL, VLDL-cholesterol and TG's in diabetic animals to nearly normal levels. There was increase in HDL-cholesterol also, was a desirable feature. The alcoholic extract of *Cucurbita maxima* had shown significant reduction in TC, LDL, VLDL and TG's and significant rise in HDL-cholesterol among the three different extracts.

Serum enzymes including, serum glutamic oxaloacetic transaminase (SGOT), serum glutamic pyruvic transaminase (SGPT), alkaline phosphate (ALP) and bilirubin are used in the elevation of hepatic disorders. Serum enzyme levels were significantly raised to high values in diabetic control animals, reflecting active liver damage or inflammatory hepatocellular disorders[36,37]. The various extracts (petroleum ether, ethyl acetate and alcohol) of *Cucurbita maxima* caused significant reduction in the activities of ALP, SGOT, SGPT and bilirubin to normal levels, showing the protective effect of the extract. The elevated levels of SGPT, SGOT reduced by the treatment of *Cucurbita maxima* which might be a consequence of the stabilization of plasma membrane as well as repair of hepatic tissue damage caused by streptozotocin. The alcoholic extract of *Cucurbita maxima* had shown significant reduction in serum ALP and bilirubin, indicated an improvement in secretory mechanism.

The phytochemical and pharmacological studies performed indicated the different extracts (petroleum ether, ethyl acetate and alcohol) of *Cucurbita maxima* contain carbohydrates, flavanoids, tannins, phenolics and saponins. Saponins appear to involve stimulation of pancreatic β-cells and subsequent secretion of insulin[38].

6. Conclusion

From the present investigation, it can be concluded that oral administration of *Cucurbita maxima* seed extracts produces significant antidiabetic effect in controlling the blood glucose level. In addition it possesses potent antihyperlipidemic effect, lowers both total cholesterol and triglycerides and at the same time increases HDL-cholesterol in STZ-induced diabetic rats and have a protective role on complications associated with diabetes. Hence, the seed extracts of *Cucurbita maxima* can be considered as a potent source of antidiabetic and antihyperlipidemic agents, which may be due to presence of flavanoids, phenols or saponins in the extract. Further studies to isolate and to

characterize the active compound and to further elucidate the mechanism involved in the antidiabetic effect are underway.

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