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CHONEMORPHA FRAGRANS (MOON) ALSTON – AN EFFECTIVE ANTIHYPERGLYCEMIC AND ANTIHYPERLIPIDEMIC AGENT IN STREPTOZOTOCIN NICOTINAMIDE INDUCED DIABETIC RATS.

Bobby S. Prasad [*1], K. K. Srinivasan [2] and Jyoti Harindran[1]

Department of Pharmaceutical Sciences [1], M. G. University, Cheruvandoor Campus, Ettumanoor, Kottayam, Kerala - 686631, India.
Department of Chemistry [2], Shri MadhwaVadiraja Institute of Technology and Management, Bantakal, Udupi, Karnataka-574115, India.

Keywords:

Chonemorphafragrans, Anti diabetic activity, Streptozotocin, Glibenclamide, Oral glucose tolerance, Normoglycemic

Correspondence to Author:
Bobby S. Prasad

Senior Lecturer,

Department of Pharmaceutical Sciences, Cheruvandoor Campus, Ettumanoor, Kottayam, Kerala - 686631, India

Email: bobyramesh@yahoo.co.in

ABSTRACT: Ethanolic extract of the roots of *Chonemorpha fragrans*, a traditionally used antidibetic plant was evaluated for its antihyperglycemic and antihyperlipidemic effect using streptozotocin-nicotinamide induced diabetic rat model. Oral glucose tolerance test with 2g/kg of glucose and normoglycemic studies were performed which showed a dose dependant decrease in sugar levels. The acute oral toxicity studies demonstrated the safety of the dose up to 2000mg/kg body weight. The diabetic rats were treated with ethanolic root extracts, at a dose of 200mg/kg and 400mg/kg based on the acute toxicity study. Standard groups were treated with Glibenclamide at a dose of 0.6mg/kg. Treatment was continued for 21 days and the weights of the rats and serum glucose levels were measured on 1^{st},7^{th},14^{th} and 21^{st}day. Other biochemical parameters like lipid profile, HbA1c, ALT, AST, serum creatinine, urea and total proteins were evaluated on the last day of the study. The results of the study have shown a significant difference between the initial and final fasting blood glucose levels of *C. fragrans* and glibenclamide treated diabetic rats. These results justifies the traditional claim of the usefulness of *C. fragrans* root extract in the treatment of type 2 *D. mellitus*.

INTRODUCTION: *Diabetes mellitus* in humans is a manifestation of metabolic disturbances due to the dietary intake of excess carbohydrates and lipids. Hyperglycemia and hyperlipidemia are important risk factors in the development of cardiovascular diseases and metabolic disorders [1]. Diabetes is a leading cause of morbidity and mortality for the world's growing population.

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The International Diabetes Federation has predicted a worldwide increase from 8.3% to 9.9% by the year 2030, with China and India projected to have the largest number of diabetic cases. Type 2 diabetes is a chronic and progressive illness that particularly targets 80% of the cases.

It is one of the primary threats to human health due to increased prevalence and associated disabling complications. At present, the treatment mainly involves a sustained reduction in hyperglycemia using oral hypoglycemic agents besides injectable insulin. However, prominent side-effects of such drugs are the main reason for an increasing number of people seeking alternative therapies that may

have less severe or no side-effects. Hence the demand has arisen for a more benign drug [2].

Chonemorpha fragrans belonging to the family, Apocynaceae, is a stout spreading lactiferous shrub with soft greyish to rusty-brown bark, flowers large, whitish to cream-yellow, fragrant [3].The roots are sweet, bitter, astringent, laxative, thermogenic, depurative, carminative, anthelmintic, digestive, antiscorbutic, sudorific, anodyne, expectorant and febrifuge. They are useful in vitiated conditions of vata and kapha, skin diseases, leprosy, scabies, syphilis, dyspepsia, flatulence, colic, constipation, helminthiasis, hyperdipsia, urethrorrhea, hyperacidity, cardiac debility, diabetes, jaundice, cough, bronchitis and intermittent fevers [4].

Chemical investigation of the of the root bark of *C. fragrans*, resulted in the isolation of japindine, N-formylchonemorphine [5], funtumafrine-C [6], and Chonemorphine [7]. The nonbasic fraction of the leaves of this plant afforded the rare Triterpenoidbaurenol acetate in addition to beta sitosterol [8]. An anticancer agent, camptothecin was isolated from the callus and stems of *Chonemorpha grandiflora* [9]. The root extract showed smooth muscle relaxant, and antiamoebic activity [10]. The alcoholic root extract was reported to exhibit hypoglycemic activity in alloxan induced diabetic rats [11]. The present study was designed to evaluate the hypoglycaemic and antihperlipidemic effect of the ethanolic extract of the roots using sreptozotocin- nicotinamide induced type 2 diabetic model.

MATERIALS AND METHODS:

Streptozotocin was purchased from Sigma Aldrich and other chemicals were purchased from Merck India Ltd.

Plant Material:

Roots of *Chonemorpha fragrans* were collected during the month of September 2010 from Thengamam, Kerala. The procured plant materials were authenticated by a botanist and a voucher specimen no. CMS-272 was deposited in the department for future reference.

Preparation of the *Chonemorpha fragrans* root extract: Shade dried roots (2 kg) were powdered and extracted with ethanol (95%) by soaking them overnight and refluxing for 3 hours and the procedure was repeated thrice. After completion of the extraction the solvent was removed by distillation and concentrated to a semisolid mass [12]. Preliminary phytochemical evaluation of the total ethanolic extract of *C. fragrans* was carried out [13].

Animals:

Wistar Albino rats were procured from the animal house of Department of Pharmaceutical Sciences, Cheruvandoor Campus, Ettumanoor. Animals were caged in polypropylene cages containing paddy husk as bedding with maximum of three animals in each cage and provided free access to standard food pellets as basal diet and water *ad libitum.* Animals were acclimatized to the experimental condition for one week. The experimental protocol was subjected to the scrutiny of Institutional Animal Ethical Committee (IAEC) of Department of Pharmaceutical Sciences (IAEC No 010/PR/UCP/CVR/11).

Acute toxicity study:

Acute toxicity studies were carried out as per Organisation for Economic Co-operation and Development guidelines 423. Alcoholic extracts of *C. Fragrans* was suspended in 0.5% CMC in distilled water and given p.o to overnight fasted rats and the animals were observed individually for their health status and signs of any abnormalities. The animals were observed for clinical signs (tremors, convulsions, lethargy and coma), gross behavioural changes and mortality after 30 min, 1, 2, 3 and 24 hr. Daily cage side observations were continued for a period of 14 days [14].

Experimental:

Oral glucose Tolerance Test (OGTT):

The OGTT was performed in overnight fasted (18hr) normal rats. Rats were grouped into four experimental groups (n=6). Control group (Group I) received an equal volume of 0.5% w/v CMC solution. Group II received glibenclamide at a dose of 0.6 mg/kg body wt. Group III and IV received ethanolic extracts of the plants at a dose of 200mg/kg and 400mg/kg respectively. Glucose (2g/kg body wt.) was given orally to all the groups half an hour after the administration of the extracts. Blood samples were collected from the tail veins of

each animal at 0 min (i.e immediately after the administration of the glucose), 60 min, 90 min, 120 min and 180 min after glucose administration and the plasma blood glucose levels were estimated using a glucometer [15].

Normoglycemic studies:

The rats were grouped into four experimental groups (n=6). Control group (Group I) received an equal volume of 0.5% w/v CMC solution. Group II received glibenclamide at a dose of 0.6 mg/kg body wt. Group III and IV received ethanolic extracts of the plants at a dose of 200mg/kg and 400mg/kg respectively. Blood samples were collected from the tail veins of each animal at 0 hr, 1hr, 2 hr, 3 hr, 4 hr after feeding the plant extracts, and the blood glucose levels were determined using glucometer after collecting the blood from the tail vein [16].

Induction of Experimental diabetes:

A rat model of type 2 *Diabetes mellitus* (noninsulin dependent diabetes mellitus, NIDDM) was induced in overnight fasted rats by a single intraperitonial (i.p.) injection of streptozotozin 60mg/kg, 15 min after the intraperitonial administration of 120mg/kg of nicotinamide in normal saline. The rats were supplied with 5% w/v glucose solution in water and standard diet during the next 24 hr to avoid sudden hypoglycemia. On day 2, glucose solution was replaced with drinking water. Blood samples were collected from the retro orbital plexus of the animals at 72hr and on day 7 after an overnight fast. Blood glucose were measured to ensure the hyperglycemia. Rats with fasting blood glucose levels above 200mg/dl were considered diabetic [17, 18].

Experimental design:

The rats were grouped into five experimental groups each consisting of 6 animals. Group I and II were considered as normal control and diabetic control. Group III was administered with Glibenclamide at 0.60mg/kg dose [19]. Group IV and V received ethanolic extracts at a dose of 200mg/kg and 400mg/kg suspended in 0.5% w/v CMC daily for 21 days to the diabetic rats. Blood samples were collected from each animal on day one, 7th day, 14th day and on 21st day from the overnight fasted animals and the blood glucose levels were determined. At the end of the experiment period, the rats were fasted overnight and blood samples were withdrawn from the retro orbital plexus of the eye using capillaries. The blood samples were analysed for various biochemical parameters like lipid profile, HbA1c, creatinine, urea, protein, ALT and AST levels. All the serum samples were estimated using an auto analyser (Coralyzer 100, Tulip Group)

Statistical analysis:

All the values of the experimental results were expressed as mean±SEM. Two-way repeated measures (mixed model) ANOVA followed by Bonferroni post hoc test was performed for normoglycemic, oral glucose tolerance test and evaluation of blood glucose of STZ-nicotinamide induced diabetic rats. One-way ANOVA followed by Tukey's multiple comparison test was applied for the statistical analysis of all the other parameters. Graph Pad Prism (version 5.01) software was used for all the statistical analysis. A difference in the mean values of $P<0.05$ was considered to be statistically significant.

RESULTS AND DISCUSSION:

Preparation of the extract:

The roots of *C. fragrans* yielded dark brown coloured semisolid and the percentage yield was found to be 6.01%w/w. Preliminary phytochemical evaluation of the total ethanolic extract of *C. Fragrans* (CFTE) showed the presence of carbohydrates, phenolic compounds, flavonoids steroids, saponins and alkaloids.

Acute Oral toxicity study:

The acute oral toxicity studies demonstrates the safety of the dose up to 2000mg/kg.

Oral Glucose Tolerance test:

Blood glucose levels of all the groups reached a maximum level at 60 minutes of glucose administration (2g/kg) and then began to decrease. As compared to the normal control all the extract treated groups and glibenclamide treated groups showed a very steep decrease in the glucose level. The ethanolic extract of the plants at a dose of 200mg/kg and 400mg/kg showed a significant decrease ($P<0.05$) in blood glucose levels when compared to the standard glibenclamide. The

extracts found to reduce the sugar levels in a dose dependant manner.

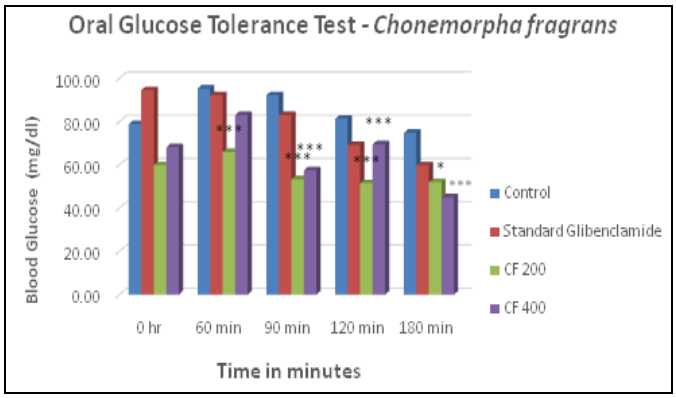

FIG. 1: ORAL GLUCOSE TOLERANCE TEST

All values are expressed as mean±SEM. n=6 n=Number of animals per treatment

*Significantly different from normal control p<0.05

Normoglycemic studies:

The normoglycemic study demonstrated that the glibenclamide and the extracts exhibited a significant reduction in blood glucose levels when compared to the normal control. This effect commenced 60 minutes after the drug administration and lasted for 4 hours.

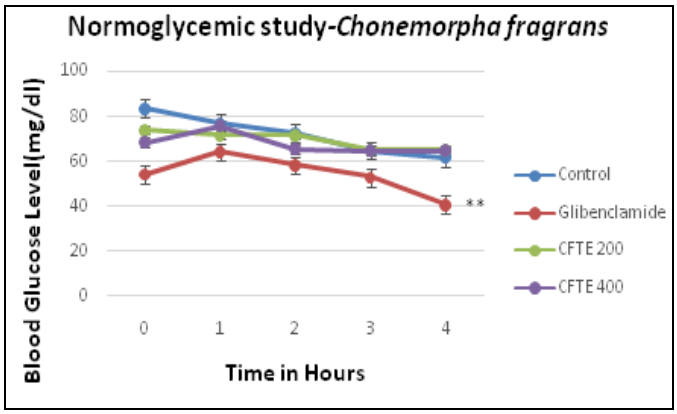

FIG.2: NORMOGLYCEMIC STUDY

All values are expressed as mean±SEM. n=6 n=Number of animals per treatment

* Significantly different from normal control p<0.05

Antidiabetic studies on Streptozotocin-Nicotinamide induced diabetic rats:

Streptozotocin(STZ) is used to induce both insulin-dependent and non-insulin dependent *Diabetes mellitus*. It causes irreversible cytotoxic effect to the pancreatic beta cells. STZ is a preferred agent to induce experimental diabetes [20]. Nicotinamide could exert a partial protection against the beta cytotoxic effect of streptozotocin. It is a direct precursor of NAD, an inhibitor of Poly (ADP-ribose) synthase enzyme activated by STZ-induced DNA injury. It also scavenges oxygen free radicals, exerts best protection when administered shortly before STZ. NAD combined with STZ shown to develop moderate and stable non-fasting hyperglycaemia without any significant change in plasma insulin level. This model appears to be closer to human type 2 diabetes than other available models with regard to insulin responsiveness to glucose and sulphonyl ureas [21].

The results of fasting blood glucose levels of STZ-NA treated diabetic rats are shown in the Table 1. The diabetic rats showed significantly elevated fasting blood glucose levels($P<0.05$) when compared to normal rats. The normoglycemic rats continued to maintain their basal blood glucose levels throughout the experiment period. The fasting blood glucose levels of the diabetic rats were elevated throughout the study but the diabetic symptoms were found to be deteriorating during the treatment period.

While the CFTE treated groups at the dose of 200mg/kg and 400mg/kg exhibited significant lowering of blood glucose levels in STZ-NA treated rats on 7th day, 14th day and 21st day. The results of the study have shown a significant difference between the initial and final fasting blood glucose levels of *C. fragrans* and glibenclamide treated diabetic rats.

TABLE 1: EFFECT OF EXTRACTS ON FASTING BLOOD GLUCOSE LEVELS

Treatment	Dose/day	Fasting blood glucose (mg/dl)±SEM			
		On day 1	On day 7	On day 14	On day 21
Normal control 0.05% CMC	2ml/kg	88.00±6.80	87.83±7.21	83.33±3.39	86.50±3.71
Diabetic control 0.05% CMC	2ml/kg	265.33±6.27	269.66±7.96	275.33±10.04	280.00±13.29
Glibenclamide	0.60mg/kg	240.16±9.88	178.66±6.92***	175.16±8.61***	133.50±11.80***
CFTE	200mg/kg	264.66±6.70	237.16±9.01***	194.83±4.81***	169.66±8.53***
CFTE	400mg/kg	296.66±15.76	269.16±8.94	229.16±15.94**	156.16±5.98***

All values are expressed as mean±SEM. n=6 n=Number of animals per treatment

*Significantly different from diabetic control p<0.05

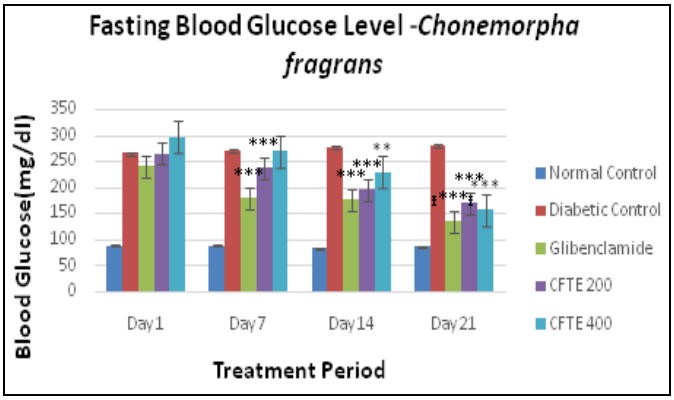

FIG.3: FASTING BLOOD GLUCOSE LEVELS

All values are expressed as mean±SEM. n=6 n=Number of animals per treatment

*Significantly different from diabetic control p<0.05

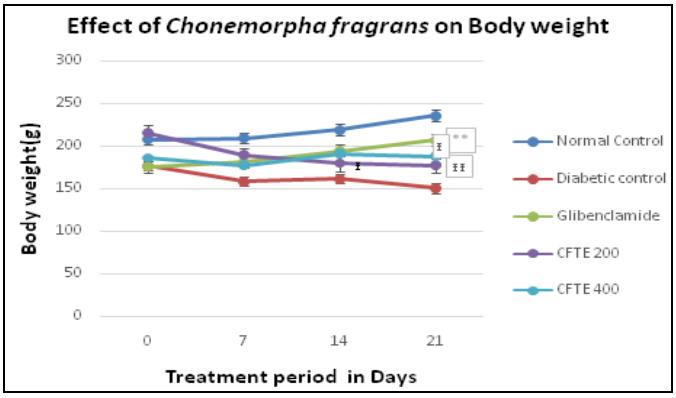

FIG. 4: EFFECT OF TREATMENT ON BODY WEIGHT

All values are expressed as mean±SEM. n=6 n=Number of animals per treatment

*Significantly different from diabetic control p<0.01

ɪ Significantly different from normal control p<0.05

In the present study the body weights of streptozotocin-nicotinamide injected rats were found to be statistically less (P <0.05) as compared to normal rats and associated with observations of diabetic symptoms like polyuria, polydipsia and polyphagia. Induction of diabetes by STZ leads to loss of body weight due to the increased muscle wasting and loss of tissue proteins [22]. The failure of diabetes animals to gain weight during the course of time is due to continuous excretion of glucose because of the defect in peripheral uptake and impairment of liver's capacity to synthesize glycogen. Body weights of all the animals were measured on 1st, 7th, 14th and 21st day. There was no lethality or toxic reaction in diabetic and treated animals during the course of study at the administered dose level.

Effect of extracts on lipid profile:

The dyslipidemic profile of diabetic rats are characterised by increase in total cholesterol, LDL, VLDL, TG and a decreased level of HDL. There was an abnormal increase in serum lipid profile in all STZ-NA diabetic rats as compared with the normal control group. Treatment with *C. fragrans* exhibited significant lowering of VLDL-C levels in STZ-NA diabetic rats at the end of treatment period. Extracts showed significant elevation of HDL cholesterol levels when compared to the diabetic group. Similarly there was a significant reduction in the elevated concentration of LDL cholesterol when compared with diabetic control at the end of treatment period. This improvement in the lipid profile of extract treated diabetic animals suggests the hypolipidemic activity of the extracts.

TABLE 2: EFFECT OF EXTRACTS ON SERUM TOTAL CHOLESTEROL LEVELS

Treatment	Dose/day (p.o)	Serum lipid parameters on day 21	
		Total cholesterol(mg/dl)	Serum glycerides (mg/dl)
Normal control 0.05% CMC	2ml/kg	55.83±1.42	58.83±1.85
Diabetic control 0.05% CMC	2ml/kg	96.00±2.08	85.00±2.42
Glibenclamide	0.60mg/kg	51.83±3.75***	56.33±4.96**
CFTE	200mg/kg	66.83±5.39***	53.50±1.61***
CFTE	400mg/kg	62.33±1.68***	55.17±6.74***

All values are expressed as mean±SEM. n=6 n=Number of animals per treatment

*Significantly different from diabetic control p<0.05

TABLE 3: SERUM LIPID PARAMETERS

Treatment	Dose/day (p.o)	Serum lipid parameters on day 21		
		HDL-C (mg/dl)	LDL-C (mg/dl)	VLDL-C (mg/dl)
Normal control 0.05% CMC	2ml/kg	51.33±0.95	7.26±0.77	11.76±0.37
Diabetic control 0.05% CMC	2ml/kg	37.67±2.91	41.33±3.05	17.00±0.48
Glibenclamide	0.60mg/kg	42.17±3.31	7.40±1.60***	11.27±0.99***
CFTE	200mg/kg	63.67±3.49ɪ**	7.53±3.72***	10.70±0.32***
CFTE	400mg/kg	58.67±1.71***	2.46±1.02***	11.03±1.34***

All values are expressed as mean±SEM. n=6 n=Number of animals per treatment

*Significantly different from diabetic control p<0.05

Effect of extracts on hepatic serum markers:
Hepatic serum markers like ALT and AST were estimated on day 21 and used for the evaluation of hepatic damage. Streptozotocin treatment has a significant role in the alteration of liver functions since the activity of AST and ALT were slightly higher than those of normal value. Treatment with CFTE showed a significant reduction of AST at a dose of 200mg/kg on comparison with diabetic control

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TABLE 4: EFFECT OF EXTRACTS ON SERUM BIOMARKERS OF LIVER

Treatment	Dose/day (p.o)	Serum biomarkers of Liver on day 21	
		AST (IU/L)	ALT (IU/L)
Normal control 0.05% CMC	2ml/kg	230.50±13.51	86.83±3.49
Diabetic control 0.05% CMC	2ml/kg	288.33±2.79	145.33±7.11
Glibenclamide	0.60mg/kg	263.00±27.40	122.67±16.40
CFTE	200mg/kg	214.17±8.80*	140.00±18.53ɪ
CFTE	400mg/kg	260.10±14.26	132.60±6.13

All values are expressed as mean±SEM. n=6 n=Number of animals per treatment
*Significantly different from diabetic control p<0.05
ɪ Significantly different from normal control p<0.05

Effect of extracts on serum biomarkers of kidney: Diabetic control showed a significant increase in creatinine and urea levels compared to control animals. The elevation of serum urea and creatinine are significant markers related to renal dysfunction in diabetic hyperglycemia [23]. Treatment with extracts significantly decreased serum creatinine levels. But the extracts did not show any significance change in urea as compared with diabetic controls.

TABLE 5: EFFECT OF EXTRACTS ON SERUM BIOMARKERS OF KIDNEY

Treatment	Dose/day (p.o)	Serum biomarkers of Kidney on day 21		
		Urea (mg/dl)	Creatinine (mg/dl)	Total protein (mg/dl)
Normal control 0.05% CMC	2ml/kg	31.67±1.28	0.70±0.00	6.07±0.28
Diabetic control 0.05% CMC	2ml/kg	61.67±0.84	0.80±0.04	6.27±0.50
Glibenclamide	0.60mg/kg	32.83±2.91***	0.70±0.05	5.47±0.19
CFTE	200mg/kg	62.33±9.07ɪ	0.94±0.18	5.88±0.14
CFTE	400mg/kg	46.33±8.10	0.77±0.05	6.43±0.25

All values are expressed as mean±SEM. n=6 n=Number of animals per treatment
*Significantly different from diabetic control p<0.05
ɪ Significantly different from normal control p<0.05

In diabetes there is an increased glycation of a number of proteins including haemoglobin. Haemoglobin is highly susceptible to non-enzymatic glycation. In diabetic condition, the excess of glucose present in the blood reacts with haemoglobin to form Glycated hemoglobin, which has altered affinity for oxygen. The glycated haemoglobin levels in the diabetic control group were significantly high as compared to the control group. Glycated hemoglobin was significantly increased in diabetic rats and this increase was directly related to elevated fasting blood glucose levels. HbA1c levels are monitored as a reliable index of glycaemic control in diabetes. Administration of the extracts to diabetic rats prevented the increase in glycosylated haemoglobin significantly and this could be due to decrease in glucose levels.

TABLE 6: EFFECT OF EXTRACTS ON GLYCATED HAEMOGLOBIN LEVELS

Treatment	Dose/day	Serum haemoglobin (HbA1c) on day 21
Normal control 0.05% CMC	2ml/kg	3.63±0.25
Diabetic control 0.05% CMC	2ml/kg	9.15±0.20
Glibenclamide	0.60mg/kg	4.90±0.76***
CFTE	200mg/kg	7.83±0.69
CFTE	400mg/kg	5.95±1.07*

All values are expressed as mean±SEM. n=6 n=Number of animals per treatment
*Significantly different from diabetic control p<0.05

CONCLUSION: Hyperglycemia and hypercholesterolemia are the two major problems with *D.mellitus* and responsible for vascular complications. It was known that the increase in glycaemia in STZ-NA induced diabetic rats is associated with dyslipidaemia characterised by elevated serum triglycerides and total cholesterol levels. In the present investigation, treatment for 21 days with ethanolic extract of *C. fragrans* showed significant antihyperglycemic and antihyperlipedimic activity. In conclusion the present study validated the traditional claims of use of root in the treatment of diabetes.

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