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EVALUATION OF ANTIDIABETIC ACTIVITY OF HYDRO ALCOHOLIC EXTRACT OF *CHRYSOPHYLLUM CAINITO* FRUITS

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ABSTRACT: Anti-diabetic activity of hydro-alcoholic extract of *Chrysophyllum cainito* frutis (CCE) was investigated against experimentally induced diabetics in rats using alloxan and streptozotocin (STZ). Acute toxicity study was performed and hydro-alcoholic extract of CCE was found to be safe at a dose of 2000 mg/kg bodyweight. Two doses 200 mg/kg and 400 mg/kg b.w p.o. of the *CCE* were subjected for the evaluation of anti-diabetic activity against the diabetic induced by alloxan (100 mg/kg, i.p) and STZ (50 mg/kg, i.p) in rats. Glibenclamide (5 mg/kg p.o) was served as standard in both the models. Fasting blood glucose, serum total cholesterol, serum triglycerides, lipid profile (HDL and LDL) and histopathology were evaluated in the study. Both the lower (200 mg/kg) and higher dose (400 mg/kg) of CCE showed a dose dependent significant decrease in blood glucose level, triglyceride, cholesterol levels and LDL and an increase in HDL in the treated diabetic rats when compared with diabetic control. Histopathology of pancreas showed regeneration of β-cells in extract treated diabetic rats. The results obtained were comparable with that of the standard drug Glibenclamide. The present study concluded that *Chrysophyllum cainito* fruits were found to be effective plant against alloxan and streptozotocin induced diabetes and also help in preservation of islet cells.

INTRODUCTION: Diabetes mellitus is a chronic disease caused by inherited and/or acquired deficiency in production of insulin by the pancreas, or by the ineffectiveness of insulin produced. Insulin deficiency results in increased concentrations of glucose in the blood, which in turn damage many of the body's systems, in particular the blood vessels and nerves [1]. Symptoms of high blood sugar include frequent urination, increased thirst, and increased hunger.

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If left untreated diabetics can cause many complications. Acute complications include diabetic ketoacidosis, nonketotic hyperosmolar coma. Serious long term complications include cardiovascular disease, stroke, kidney failure, foot ulcers and damage to the eye [2]. The long–term effects of diabetes mellitus include progressive development of the specific complications of retinopathy with potential blindness, nephropathy that may lead to renal failure, and/or neuropathy with risk of foot ulcers, amputation, Charcot joints, and features of autonomic dysfunction, including sexual dysfunction. People with diabetes are at increased risk of cardiovascular, peripheral vascular and cerebrovascular disease [3].

The number of people with diabetes has risen from 108 million in 1980 to 422 million in 2014. The

global prevalence of diabetes among adults over 18 years of age has risen from 4.7% in 1980 to 8.5% in 2014 [4]. Diabetes mellitus has recently been identified by Indian Council of Medical Research (ICMR) as one of the refractory diseases for which satisfactory treatment is not available in the modern allopathic system of medicine [5]. Currently available synthetic antidiabetic agents produce serious side effects like hypoglycemic comaand hepatorenal disturbances. Moreover, they are not safe for use during pregnancy [6]. Hence, the search for safer and more effective hypoglycemic agents has continued. Following the WHO's recommendation for research on the beneficial uses of medicinal plants in the treatment of diabetes mellitus, investigations on hypoglycemic agents derived from medicinal plants have also gained momentum [7].

Chrysophyllum cainito (Family Sapotacae), commonly known as star apple, grown in warm temperatures that do not dip below freezing. *Cainito*s require dry seasons and very rainy wet seasons in order to thrive. Examples of states in India most conducive to growing star apples are Tamil Nadu, Andhra Pradesh, Kerala, Goa and Maharashtra. *Cainito* trees bear fruit in February and March [8].

While reviewing the available information for selecting folklore based remedy for the evaluation of anti-diabetic activity of fruits of *Chrysophyllum cainito* (Family Sapotacae), are found to be used for this purpose in folklore medicine in some parts of the country. *Chrysophyllum cainito* fruit contained phytochemical constituents like catechin, epicatechin, gallocatechin, gallic acid, epigalocatechin. Fruits contained phyto-constituents like flavonoids, tannins, alkaloids which are renowned for anti-oxidant activity. However, no published data is available to prove the folklore claim as antidiabetic.

Based on these backgrounds, in the present the hydro-alcoholic extract of fruits of *Chrysophyllum cainito* was selected to screen against experimentally induced diabetes mellitus.

MATERIALS AND METHODS:

Plant material: The fruits of *C. cainito* have been collected from Kannur district, Kerala and authenticated by Taxonomist. The fruits were dried under shade. The dried fruits were pulverized separately into coarse powder by a mechanical grinder and passed through a sieve (BSS no. 10), and used for extraction.

Preparations of Extracts: [9] Hydroaclcoholic extracts of the dried fruits were done by the continues hot percolation method using soxhlet apparatus. The powdered material (150 g) of *C. cainito* fruits were packed in soxhlet extractor and extracted using water and ethanol (1:1 ratio) as solvent. The temperature was maintained on an electric heating mantle with thermostat control. Appearance of colorless solvent in the siphon tube was taken as the termination of extraction. The extract was concentrated by using rotary flash evaporator. The concentrated extract was then air dried at room temperature, weight and percentage yield was calculated. Extracts were stored in a desiccator and used for subsequent experiments.

Preliminary Phytochemical Screening: [10] The hydroalcoholic extract of the fruits was subjected to preliminary phytochemical screening for detection of major chemical constituents.

Experimental Animals: Healthy Wistar albino rats (150–200 g) of either sex were used for the experiments. They were procured from the animal house of Srinivas College of Pharmacy, Mangalore. The animals were maintained under standard conditions (temperature 22 ± 2^{o}C, relative humidity 60 ± 5% and 12 h light/dark cycle). The animals were housed in sanitized polypropylene cages. They had free access to standard pellet diet (Hindustan Lever Ltd., Mumbai, India) and water *ad libitum*. The Institutional Animal Ethics Committee approved the experimental protocol (SCP/CPCSEA/F150/P04/2015).

Acute Toxicity (LD_{50}) studies: [11]

The toxicity studies were carried out according to OECD guidelines-425. Female Wistar albino rats weighing between 150-200 g were used to carry out acute toxicity studies. The animals were given Hydro-alcoholic extract of *C. cainito* fruits. After the sighting study, starting dose of 2000 mg/kg (p.o.) of the test samples was given to various groups containing five animals in each group.

The animals were observed continuously for 4 h for any behavioral, neurological profiles, spontaneous activity, reactivity, and any mortality.

Anti-diabetic Activity:

Alloxan induced anti-diabetic activity: [12, 13] Hyperglycemia was induced by single i.p injection of 100 mg/kg of alloxan monohydrate in normal saline. Fasting blood glucose was determined after depriving food for 16 h with free access to drinking water. After 2 days of alloxan injection, the hyperglycemic rats (glucose level >200 mg/dl) were separated and divided into five groups consisting of six rats in each group for the anti-diabetic study. The treatment was started from the same day except diabetic control groups. The animals had free access to feed and water *ad libitum*. The animals were treated as follows,

Group I: Normal control (Vehicle)

Group II: Alloxan + Vehicle (Diabetic control)

Group III: Diabetic animals treated with *Chrysophyllum cainito* fruit extract (CCE) (200 mg/kg)

Group IV: Diabetic animals treated with CCE (400 mg/kg)

Group V: Alloxan + Glibenclamide (5 mg/kg/day, p.o.) and served as standard.

Streptozotocin induced anti-diabetic activity: [14] Hyperglycaemia was induced by single i.v injection of 50 mg/kg of STZ in normal saline, freshly prepared and injected within 5 minutes of preparation to prevent degradation. After administration of STZ the animals had free access to feed and water ad libitum. Fasting blood glucose was determined after depriving food for 16 h with free access to drinking water. The development of hyperglycaemia in rats was confirmed by fasting blood glucose estimation 48 h post STZ injection. The rats with fasting blood glucose level of above 200 mg/dl at 48 h after STZ injection were considered diabetic and included in study. The animals were treated as follows,

Group I: Served as normal control (normal saline)

Group II: STZ+ Normal saline (Diabetic control)

Group III: Diabetic animals treated with CCE (200 mg/kg)

Group IV: Diabetic animals treated with CCE (400 mg/kg)

Group V: STZ+ Glibenclamide (5 mg/kg/day, p.o.) and served as standard.

The above treatment was carried out in each group of animals for both the models for 30 days. Fasting blood glucose was measured using glucostrip with glucometer. Blood samples were withdrawn under mild anaesthesia from tail vein of the overnight fasted animals on 1^{st}, 7^{th}, 14^{th}, 21^{st} and 30^{th} day. The animals were sacrificed on 30^{th} day after the blood collection for biochemical estimations by retro orbital puncture and pancreas were removed for histopathological studies. The serum was obtained by centrifuging the blood samples at 3000 rpm for 10 min and they were used for estimation of lipid profile, cholesterol and triglycerides. Pancreatic tissues from all groups were subjected to histopathological studies.

Statistical analysis: The values are expressed as mean ± SEM. The results were analyzed for statistical significance using one-way ANOVA, followed by Dunnet's test. $P < 0.05$ was considered significant.

RESULTS: Preliminary phytochemical screening of the extract of C. *cainito* revealed the presence of alkaloids, glycosides, proteins and amino acids, sterols, carbohydrates, phenolic compounds, flavonoids, saponins and tannins.

Acute toxicity studies: All extract treated rats showed no discernible behavioral changes up to 2000 mg/kg by oral route. All the animals were alive, healthy, and active during the observation period. No mortality was observed at this dose during the observation period. Acute toxicity studies revealed the nontoxic nature of the extract.

Alloxan induced antidiabetic activity: Fasting blood glucose level (FBG) was within the range of 70-90 mg/dl in all the groups at day 0. Treatment with alloxan in normal saline (100 mg/kg, i.p) had increased the FBG level more than 200 mg/dl after 48 h. Changes in FBG level in different groups after repeated dose administration are tabulated in **Table 1**. Diabetic control group has showed significant increase in fasting blood glucose during the study period.

Glibenclamide (5 mg/kg) significantly (p<0.01) reduced FBG after repeated administration as compared to diabetic control group. Whereas treatment with CCE at dose 200 mg/kg and 400 mg/kg has significantly (p<0.01) decreased FBG as compared to diabetic control on 7th, 14th, 21st and 30th day.

Strpetozotocin induced antidiabetic activity: Fasting blood glucose (FBG) level was within the range of 75-90 mg/dl in all the groups at day 0. Treatment with STZ in normal saline (50 mg/kg, i.p.) had increased the FBG level more than 200 mg/dl after 48 h. Changes in FBG level in different groups after repeated dose of drug administration are tabulated in **Table 2**. Diabetic control group has showed significant increase in fasting blood glucose during the study period. Glibenclamide (5 mg/kg) significantly (p<0.01) reduced FBG after repeated administration as compared to diabetic control group. Whereas treatment with CCE at dose of 200 mg/kg and 400 mg/kg has significantly (p<0.05) decreased FBG as compared to diabetic control on 7th, 14th, 21st and 30th day.

Both the doses of CCE significantly (p<0.05) decreased the elevated levels of TC, TG, and LDL, and increased HDL level in both the diabetic rats. These parameters were significantly (p<0.05) different in the diabetic treated rats when compared to the diabetic control groups.

TABLE 1: EFFECT OF *CHRYSOPHYLLUM CAINITO* FRUIT EXTRACT ON BLOOD GLUCOSE LEVEL IN ALLOXAN INDUCED DIABETIC RATS.

Groups	Blood glucose level (mg/dl)				
	Initial	Day 7	Day 14	Day 21	Day 30
Normal control	75.33±7.50	72.31±1.145	71.69±12.12	75.98±10.132	73.24±12.31
Diabetic control	268.17±12.75	293.14±12.35	299.5±2.432	326.8±10.12	315.5±2.513
Glibenclamide (5 mg/kg)	270.50±20.83	198.53±8.321**	151.0±7.625***	115.8±9.347***	101.5±3.096***
CCE (200 mg/kg)	267.67±24.43	251.89±5.266*	218.2±7.059*	190.8±10.28**	154.7±2.418**
CCE (400 mg/kg)	265.7±5.725	238.14±6.491*	193.7±12.31**	165.0±5.774**	129.2±2.960**

Values are expressed as mean ± SEM. n = 6 for each group. *p<0.05, **p<0.01, ***p<0.001. One way ANOVA followed by Dunnet's test compared to diabetic control.

TABLE 2: EFFECT OF *CHRYSOPHYLLUM CAINITO* FRUIT EXTRACT ON BLOOD GLUCOSE LEVEL IN STZ

Groups	Blood glucose level (mg/dl)				
	Initial	7th day	14th day	21st day	30th day
Normal control	77.50±1.78	76.01±3.08	78.01±5.22	76.05±6.36	77.58±1.248
Diabetic control	323.12±1.52	350.7±7.17	362.2±2.65	355.25±1.25	338.87±5.43
Glibenclamide (5mg/kg)	320.0±6.158	265.8±5.16**	208.5±10.2**	127.8±2.58***	105.2±4.1***
CCE(200 mg/kg)	325.85±3.95	298.2±5.57*	226.4±9.15**	192.9±8.65**	144.3±2.56**
CCE(400 mg/kg)	326.31±6.35	276.0±3.95*	215.8±1.24**	149.65±5.326**	122.5±1.501**

Values are expressed as mean ± SEM. n = 6 for each group. *p<0.05, **p<0.01, ***p<0.001. One way ANOVA followed by Dunnet's test compared to diabetic control.

TABLE 3: EFFECT OF CCE ON SERUM CHOLESTEROL, TRIGLYCERIDES, HDL AND LDL IN ALLOXAN INDUCED DIABETIC RATS.

Groups	Serum			
	Cholesterol (mg/dl)	Triglyceride(mg/dl)	HDL(mg/dl)	LDL (mg/dl)
Normal control	88.32±0.935	64.02±1.25	40.20±1.302	42.01±0.145
Diabetic control	185.25±2.102	155.89±0.455	16.52±0.861	117.24±0.37
Glibenclamide (5 mg/kg)	102.58±0.935**	72.33±1.63**	32.33±0.58**	63.25±1.07**
CCE (200 mg/kg)	130.10±0.142**	102.3±0.571**	21.35±0.487*	78.08±0.254**
CCE (400 mg/kg)	112.16±0.578**	91.09±0.357**	29.15±0.14**	70.21±1.652**

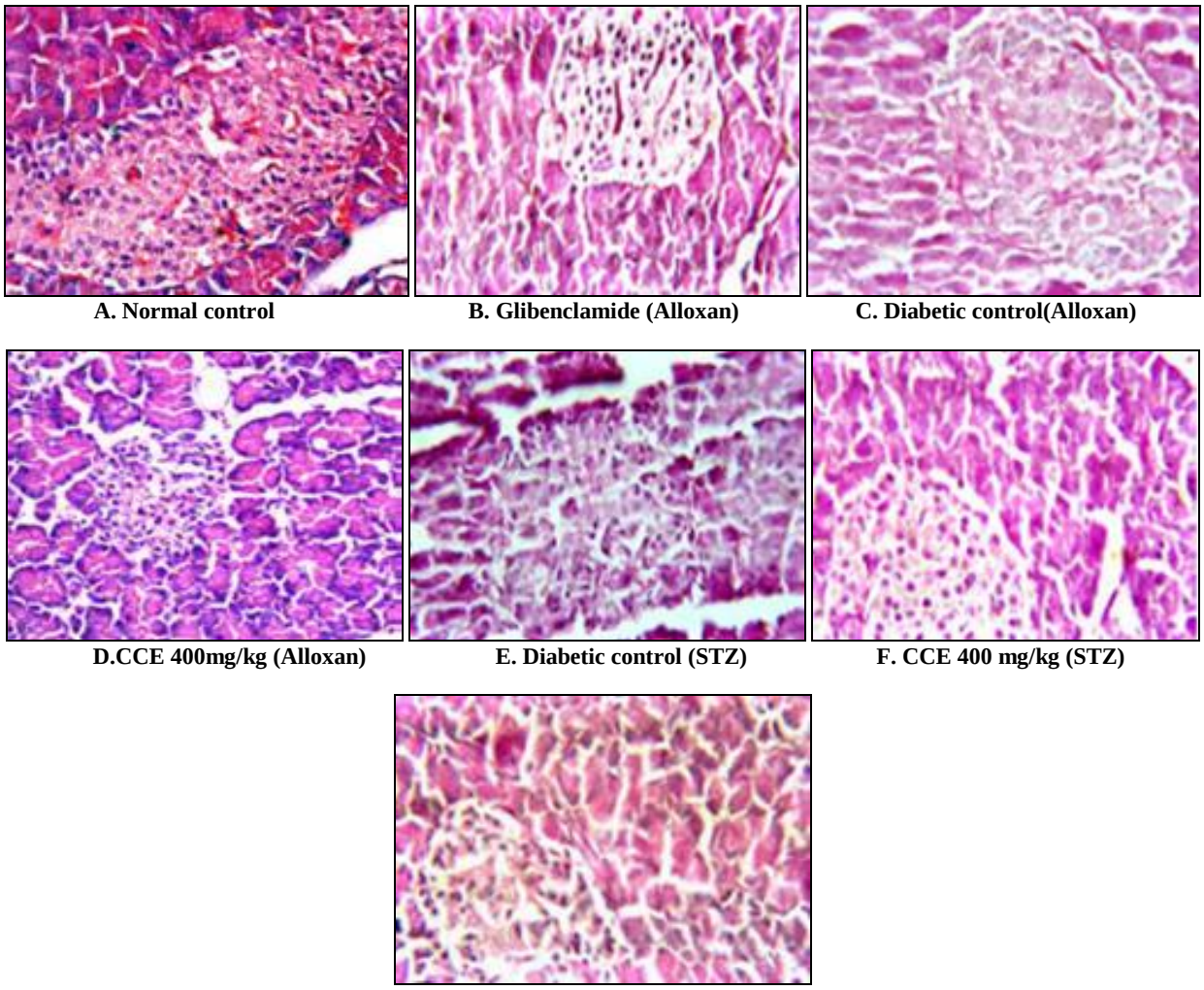
Values are expressed as Mean± S.E.M (n=6). One way ANOVA followed by Dunette's test. *p<0.05, **p<0.01 when compared with diabetic control group.

TABLE 4: EFFECT OF CCE ON SERUM CHOLESTEROL, TRIGLYCERIDES, HDL AND LDL IN STZ INDUCED DIABETIC RATS.

Groups	Serum			
	Cholesterol	Triglycerides	HDL	LDL
Normal control	82.23±2.153	67.58±0.05	42.25±1.54	43.89±3.217
Diabetic control	183.5±0.124	163.26±1.69	19.86±8.12	125.21±1.58

Glibenclamide (5mg/kg)	95.7±1.59***	75.4±3.254***	39.89±4.25***	51.32±2.68***
CCE(200 mg/kg)	138.3±0.258*	105.0±6.18**	27.57±3.51*	106.98±1.951*
CCE(400 mg/kg)	110.6±6.12**	96.8±893**	31.75±0.24**	86.01±2.68**

Values are expressed as Mean± S.E.M (n=6). One way ANOVA followed by Dunette's test. *p<0.05, **p<0.01 when compared with diabetic control group.



A. Normal control **B. Glibenclamide (Alloxan)** **C. Diabetic control(Alloxan)**

D.CCE 400mg/kg (Alloxan) **E. Diabetic control (STZ)** **F. CCE 400 mg/kg (STZ)**

G. Glibenclamide (STZ)

FIG. 1 (A-G): DEPICTS THE ISLETS OF THE PANCREAS OF RATS IN DIFFERENT GROUPS. PHOTOMICROGRAPHS (A) OF THE NORMAL, HEALTHY CONTROL GROUP SHOWED NORMAL ACINI AND NORMAL CELLULAR POPULATION OF THE ISLETS OF LANGERHANS. TREATMENT OF DIABETIC RATS WITH GIBENCLAMIDE SHOWED MODERATE EXPANSION OF CELLULAR POPULATION AND SIZE OF ISLET CELLS (B &G). HOWEVER, THE EXTRACT TREATED-DIABETIC RATS(D&F) SHOWED PARTIAL RESTORATION OF THE NORMAL CELLULAR POPULATION AND SIZE OF ISLET CELLS IN BOTH OF THE CASES

DISCUSSION: This study was carried out to investigate the effects of *Chrysophyllum cainito* fruit extract on blood glucose level and lipid profile of diabetic rats. From results obtained, Alloxan monohydrate selectively destroyed the pancreatic beta cells of the rats used causing marked degeneration of the islets of langerhans which lowered insulin secretion with reduction in the rate of conversion of glucose to glycogen. The result of which is the marked increase of sugar level (hyperglycaemia) in the diabetic rats.

The result agrees with already existing literature that Alloxan induces diabetes mellitus by selectively destroying the beta cells of the pancreas which are involved in the synthesis of, storage and release of insulin, the peptide hormone regulating carbohydrate, protein and lipid metabolism, leading to marked increase in blood glucose concentration observed in the rats after administration and confirms the development of diabetes mellitus [15].

The mechanisms by which Streptozotocin brings about its diabetic state include selective destruction of pancreatic insulin secreting β-cells, which make cells less active and lead to poor glucose utilization by tissues [16].

Glibenclamide was used as a standard because it is a second generation sulfonylurea derivative, oral hypoglycaemic agent and found to be effective in diabetic rats that retain functioning of islet β-cells. Hence the principle mechanism of action is to stimulate the production and secretion of insulin by the β-cells of pancreas. This drug may lower down the output of glucose from the liver by insulin independent mechanism [17].

Hydro-alcoholic extract of *Chrysophyllum cainito* fruits showed significant ($p<0.01$) antidiabetic activity in both the experimentally induced diabetes models, which were compared to standard Glibenclamide. The results in the present study indicate that the fruits of *Chrysophylum cainito* were found to be effective against both alloxan and streptozotocin induced diabetes.

The diabetic control rats had elevated mean total cholesterol, triglycerides (TG), low density lipoprotein cholesterol (LDL-C) with decreased high density lipoprotein cholesterol (HDL-C). All doses of *C.cainito* and Glibenclamide significantly ($p<0.05$) reduced cholesterol, Triglycerides, LDL-C and significantly increased the HDL-C level in the diabetic treated rats. These results indicated that the hydro-alcoholic extract of fruits of *C. cainito* possessed hypolipidemic effect in diabetic treated rats.

Histopathological studies of pancreas also supported our findings. Photomicrographs showed normal acini and normal cellular population in the islet of Langerhans in pancreas of normal control rats. The islets were extensively damaged and with reduced dimensions in the diabetic control group. Glibenclamide treated group suggests restoration of normal cellular size of islets. CCE treated group showed possible partial restoration of the islets of Langerhans cells.

C. cainito fruit extract was screened for phytochemical principles and yielded alkaloids, flavonoids, polyphenols and carbohydrates.

Previous diabetic researchers reported that, the alkaloids and flavonoids are involved in the antidiabetic activity. Alkaloids would be used as stimulatives of the hepatic glycogenogenesis [18]. Flavonoids are known to be bioactive antidiabetic principles [19]. Alkaloids, flavonoids and other polyphenols present in the fruits of this plant might be responsible for the observed antidiabetic effect. The exact mechanism of antidiabetic potentials is not clear.

However, the significant antidiabetic effect of extract of *C. cainito* fruits might be due to the potentiation of serum insulin effect by increasing either the pancreatic secretion of insulin from the existing β-cells or by increasing the peripheral utilization of glucose and inhibiting the glucose transporter activity from the intestine.

CONCLUSION: From experimental data it can be concluded that the hydro-alcoholic extract of the *Chrysophyllum cainito* fruits showed significant, dose-dependent anti-diabetic activities in both alloxan and STZ induced diabetic models. The possible mechanism of action might be due to the regeneration of pancreatic β-cells as seen in histopathological studies, which may increase the insulin level or by increasing the peripheral utilization of glucose. Though the extract showed significant anti-diabetic activity, further study is needed to isolate the bioactive compounds responsible for this activity with exact mechanism of action.

CONFLICT OFINTRESTS: We declare that we have no conflict of Intrests.

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