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Antidiabetic, Antihyperlipidemic and Renal Protective Activities of *Garcinia indica* Linn. Clusiaceae

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ABSTRACT

To investigate the antidiabetic, antihyperlipidemic and renal protective activities of the aqueous and ethanol extract of *Garcinia indica* fruit rinds against alloxan induced diabetes in rats. Wistar rats were made diabetic by a single dose of alloxan hydrate [130 mg/kg *i.p.*]. After the successful induction of experimental diabetes, rats were divided into five groups each comprising a minimum of six rats. The effects of extracts and glibenclamide on fasting blood glucose, plasma lipid levels and renal profile were examined for 21 days. Blood glucose levels and biochemical parameters such as serum cholesterol, triglycerides, HDL-cholesterol, LDL-cholesterol, urea and creatinine levels of rats were measured using on weekly intervals i.e day 0, 7, 14 and 21 after daily administration of all extracts at dose of 500 mg/kg. Statistical analysis was performed using Dunnett's test. $p < 0.01$ was taken as the criterion of significance. Oral administration of both aqueous and ethanol extract for 21 days caused a significant [$p < 0.01$] reduction in blood glucose levels, lipid profile except HDL; urea and creatinine in diabetic rats. *Garcinia indica* fruit rind possesses antihyperglycemic activity as well improves total lipid levels and renal profile. It can justify folklore uses of the plant in diabetes.

Keywords: Alloxan hydrate, antihyperglycemic, lipid profile, renal profile.

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INTRODUCTION

disorders

characterized by abnormal carbohydrate, fat and

protein metabolism, which results most notably in hyperglycemia due to defects in insulin secretion, insulin action, or both. ^[1] Insulin deficiency results in

severe hyperglycemia which triggers complications involving dyslipidemia, obesity, coronary heart disease, macroangiopathy, retinopathy, cataract formation, peripheral nerve damage, nephropathy, endothelial dysfunction and eventual failure of various organs, especially the eyes, kidneys, nerves, heart, and brain. [2-5] The number of people suffering from diabetes worldwide is increasing at an alarming rate. Diabetes mellitus is a common health problem throughout the world. According to the World Health Organization statistics, the global prevalence of diabetes mellitus is approximately 155 million, which is expected to increase to 300 million in the year 2025. [6] Reasons for this rise include increase in sedentary lifestyle, consumption of energy rich diet, obesity, higher life span etc. [7] Besides the use of insulin for the treatment of insulin dependent diabetes mellitus [IDDM], other approaches for the control of hyperglycemia include the use of amylin analogues which regulate gastric emptying and inhibitors of intestinal alpha glucosidases like acarbose, miglitol and voglibiose which delay postprandial hyperglycemia. Sulphonylureas, the most widely used class of drugs act by closure of ATP sensitive K⁺ channel. Metformin, a biguanide oral antidiabetic drug limits intestinal glucose absorption. These drugs have certain effects like causing hypoglycemia at higher doses, insulin allergy, resistance, edema, lipodystrophy, liver problems, cardiotoxicity, lactic acidosis and diarrhea. It is apparent that due to the side effects of the currently used drugs, there is a need for a safe agent with minimal adverse effects, which can be taken for long durations. [8-9]

Herbal medicines are the oldest remedies known to mankind. In the present scenario, the demand for herbal products is growing exponentially throughout the world and major pharmaceutical companies are currently conducting extensive research on plant materials for their potential medicinal value. In many journals, national and international, we find an increasing number of research publications based on herbal drugs. Many analysis-based studies regarding pharmacological research in India have been conducted in the past. [10] Few of plants used for the treatment of diabetes have received scientific and medical scrutiny and even the WHO expert committee on diabetes recommends that this area warrant further attention. [11] Kokum [*Garcinia indica Choisy*] belongs to mangosteen family [Clusiaceae], which is a very large genus of polygamous perennial trees and shrubs, native to Asia, South Africa and Polynesia. The tree grows expansively in the Konkan region of Maharashtra, Goa, coastal areas of Karnataka and Kerala, Andaman and Nicobar Islands, forests of Assam, West Bengal and Gujarat. [12] The seeds are a rich source of kokum butter, which is nutritive, demulcent, smoothening, softening etc. and used for cosmetic, confectionary and culinary purposes. *Garcinia indica Choisy* has been suggested in the Indian

system of medicine as an infusion, in skin rashes caused by allergies, treatment of burns, to relieve sunstroke, remedy for dysentery, an appetizer, liver tonic, to allay thirst and as a cardiotonic. [13-15] Raw fruits, young leaves and bark are also used as medications against several disorders. [16] Some pharmacological effects of *Garcinia indica* fruit rinds have also been demonstrated, such as antimicrobial, cytotoxic, antioxidant, hepatoprotective, antiulcer, antidepressant and anxiolytic activities. [17-22] Research articles that have reported effects induced by *Garcinia indica* fruit rinds extracts include antitumor activity, cardioprotective, immunomodulatory, antiobesity, and free radical scavenging potential. [23-27] *Garcinia indica* is a rich source of active compounds including garcinol, polyisoprenylated benzophenones, isogarcinol, camboginol xanthochymol, and isoxanthochymol. [28-29] The fruits contain citric acid, acetic acid, malic acid, ascorbic acid, hydroxycitric acid and garcinol. [30-31] The rind of ripe Kokum fruits consists of a mixture of two anthocyanins namely, cyanidin-3-sambubioside and cyanidin-3-glucoside. [32-33] Anthocyanin, Cyanidin 3-glucoside ameliorates hyperglycemia and insulin sensitivity. [34] *Garcinia indica* fruit rinds contain these active constituents. There is no systematic and scientific investigation for antidiabetic activity has been conducted on this plant. Hence, this study has been conducted to evaluate antidiabetic, antihyperlipidemic and renal protective properties of the aqueous and ethanol extract of *Garcinia indica choisy* fruit rinds against alloxan induced diabetes in rats.

MATERIALS AND METHODS

Chemicals

Alloxan hydrate was purchased from Research Lab Fine Chem Industries, Mumbai. One touch glucometer [Accu-check sensor] was purchased from Roche Diagnostics, Germany for determination of blood glucose levels and Uristix was purchased from Bayer Diagnostics India Ltd.

Plant material

The *Garcinia indica* Linn fruits were collected from the Devrukh region in Ratnagiri district Maharashtra and taxonomically identified and authenticated from Dr. Yadav, Department of Botany, Willington College, Sangli (Voucher specimen no. BN 286).

Preparation of aqueous extract of *Garcinia indica* Linn fruit rind

Fruits were cut open and the seeds were separated from the pulp. Then the fruit rinds were allowed to dry in the shade. The fruits rinds were cut into pieces and shade dried at room temperature. The dried fruits were subjected to size reduction to a coarse powder by using mixer grinder. The coarsely powdered form of shade dried fruit rinds was placed in a conical flask containing distilled water and closed with cotton plug for 7 days at room temperature. Then it was filtered using a piece of clean, sterile, white cotton cloth and evaporated to dryness to yield aqueous extract. The

semisolid extract obtained was stored in an airtight container in refrigerator for further use. 20 g of dried leaves powder used for extraction that has given 1.4 g of water extract [7%]. The solution of aqueous extract was prepared by using distilled water as solvent for experiment.

Preparation of ethanolic extract of *Garcinia indica* Linn fruit rind

The fruits rinds were cut into pieces and shade dried at room temperature. The dried fruits were subjected to size reduction to a coarse powder by using mixer grinder. This powder was defatted with petroleum ether then filtered. The residue was allowed to dry at room temperature. This residue was extracted with ethanol [95%] into Soxhlet apparatus. The extract was dried at room temperature till semisolid mass was obtained. The sweet scented, chocolate colored semisolid residue formed after the complete dryness was kept in an airtight and waterproof container, which is stored in the refrigerator. The suspension of ethanol extract of *Garcinia indica* Linn fruit rind was prepared in 0.5% w/v carboxymethylcellulose in distilled water.

Preliminary phytochemical screening

A portion of residue from each extract was subjected to phytochemical analysis to test the presence of carbohydrates, glycosides, alkaloids, flavonoids, tannins, sterols and triterpenoids in the leaves extracts. [35]

Acute toxicity study

Animals were fasted for 3-4 h prior to dosing. Following the period of fasting, all extracts at doses of 200, 300, 600, 1000, 2000 and 5000 mg/kg body weight were administered to six groups with 6 rats each. Animals were observed individually after dosing at least once during the first 30 min. periodically during the first 24 h, with special attention given during the first 4 h. Time of onset and length of recovery period were observed. Additional observations include change in skin and fur, eyes and mucous membranes, and also somatomotor activity and behavior pattern. Attentions were given to observations of tremors, convulsions, salivation, diarrhea, sleep and coma. [36]

Animals

Male/female Wistar albino rats weighing 180-200 g, procured from the animal house of Pharmacology department, Appasaheb Birnale College of Pharmacy, Sangli were used with the approval of The Institute Animal Ethics Committee. During the complete course of the experiment, rats were maintained at room temperature in the animal house. The animals had free access to food pellets [Amrut Laboratories animal feed, Sangli, India] and water *ad libitum*. Each group of animals was housed separately with a distinct identity throughout the study. Throughout, internationally accepted ethical guidelines for the care of laboratory animals were followed in the study period [IAEC No.843/AC/CPCSEA].

Induction of diabetes in rats

The alloxan hydrate solution was freshly prepared in saline solution, kept on ice and injected immediately. Male/female Wistar Albino rats, weighing between 180-200 g, were selected and marked for individual identification. Rats were fasted for at least 16 h because fasted animals are more susceptible to alloxan. [37-38]

Hyperglycemia was induced by injecting alloxan hydrate at a dose of 130 mg/kg intraperitoneally for low mortality. [39-40] 10% dextrose was there after administered orally since alloxan is capable of producing fatal hypoglycemia as a result of massive pancreatic insulin release. [41-42] Rats that died during the experiment were excluded from the analysis. Then 5 days later blood samples were collected and glucose levels were determined by using Accu check glucometer to confirm the development of diabetes. The mortality rate of rats was observed about 20%. Five days after alloxan injection, rats with fasting blood glucose level >300 mg/dl were included in further study.

Experimental design

All the diabetic animals were divided in to the five groups with six animals in each group.

Group I: Vehicle [Non-diabetic] control received distilled water [10 ml/kg *p.o.*]

Group II: Diabetic control received 0.5% w/v carboxymethylcellulose in distilled water

Group III: Diabetic rats received standard drug glibenclamide [10 mg/kg *p.o.*]

Group IV: Diabetic rats received aqueous extract of *Garcinia indica* fruit rinds [500 mg/kg *p.o.*]

Group V: Diabetic rats received ethanol extract of *Garcinia indica* fruit rinds [500 mg/kg *p.o.*]

The drug solutions or vehicle were administered orally by gastric intubation once daily at 11 AM for 21 days. The effect of vehicle, extract and standard drug on blood glucose and other biochemical parameters was determined in animals at 0, 7, 14, 21 day after oral administration.

Assessment of biochemical parameters

Blood sample was collected from retro orbital plexus with the help of a capillary tube into the EDTA sprinkled tubes from overnight fasted rats and were centrifuged at 3000 rpm for 20 min. Fasting blood glucose level of the rats was recorded by Accu-check glucometer. Serum was separated and stored at -20°C until analysis was performed. Serum samples were analyzed for cholesterol, HDL, urea, creatinine and triglycerides using BTS 350 Semi-automated analyzer [Biosystem, Spain]. LDL was calculated using following formulae:

$$LDL = TC - [TG/5 + HDL]$$

Statistical analysis

One way analysis of variance [ANOVA-Dunnett test] was performed. All the values of fasting blood glucose and biochemical estimations were expressed as mean $\pm$ standard error of mean [S.E.M.]. $P < 0.01$ was considered as the criterion of significance. The statistical analysis was carried out by the Graph Pad INSTAT 3.0 software.

RESULTS AND DISCUSSION

The preliminary phytochemical investigation aqueous and ethanol extract of *Garcinia indica* Linn fruit rind indicate the presence of flavonoids, saponin glycosides, alkaloid, tannins and phenolic compounds. The fruit rinds of *Garcinia indica* have reported to contain anthocyanin flavonoid, cyanidin 3-glucoside that ameliorates hyperglycemia and insulin sensitivity due to its antioxidant activity. [34,43] In the present study, we have investigated effect of *Garcinia indica* Linn fruit rind extracts on fasting blood glucose and serum biochemical parameters [lipid profile and renal profile] in alloxan induced diabetic rats.

Fasting blood glucose

It has also been shown that alloxan induces its diabetogenic activity mainly by inducing oxygen free radicals and thereby produces selective cytotoxicity in pancreatic β -cells of Langerhans resulting in reduced synthesis and release of insulin. [44-46] Administration of alloxan hydrate [130 mg/kg, *i.p.*] led to 5-6 fold elevation of fasting blood glucose levels when compared to normal rats, which was maintained over a period of three weeks. Alloxan treated rats exhibit severe hyperglycemia, glycosuria, unexpected weight loss, hyperlipidemia, polyuria, polyphagia, polydipsia and other symptoms of uncontrolled diabetes. [47] Effect of daily dose of AEGI, EEGI and glibenclamide on blood glucose levels in alloxan induced diabetic rats is given in Table 1.

In present study, aqueous extract, ethanol extract and glibenclamide showed rapid normalization of blood glucose levels while hyperglycemia was maintained in diabetic control group throughout the total duration of the study. It is possible that both aqueous extract and glibenclamide bring about release of insulin from the surviving β -cells, thereby, resulting in normalization of blood glucose levels. Ethanol extract also showed reduction in fasting blood glucose level but did not significantly bringing to normal.

Hyperglycemia results in the generation of free radicals, which can exhaust antioxidant defenses thus leading to the disruption of cellular functions, oxidative damage to membranes and enhanced susceptibility to lipid peroxidation. [48-49] Hyperglycemia increases the production of free radicals and reactive oxygen species by glucose autooxidation, advanced glycation end products, polyol pathway [increased glucose flux through the aldose reductase pathway], non-enzymatic protein glycosylation, impaired glutathione metabolism, lipid peroxides formation, cellular oxidation/reduction imbalances, reduction in cellular antioxidant levels that dispose of free radicals like superoxide dismutase [SOD], glutathione peroxidase [GPx] and catalase and intracellular accumulation of lipids and metabolic alterations all lead to the increased formation of oxygen derived reactive oxygen which are known to abrogate the metabolic effects of insulin. Due to these events, the balance normally present in cells between free radical formation and antioxidant

protection against them is disturbed. The mitochondrial leakage of these reactive oxygen species leads to oxidative damage of cell components such as proteins, lipids and nucleic acids. In both insulin dependent [type I] and non-insulin dependent diabetes [type II] there is increased oxidative stress. [50] Antioxidant treatment can exert beneficial effects in diabetes, with preservation of in vivo β -cell function. Antioxidant treatment suppresses apoptosis in β -cells without changing the rate of β -cell proliferation. They work in synergy with each other and against different types of free radicals. [51-54] In this study we suggest that the possible mechanism of action by extracts could be related to antioxidants activity that aid to recover from impaired metabolism of glucose. Previous studies have demonstrated that *Garcinia indica* fruit rinds have potential antioxidant activity. [55]

Lipid profile

The impairment of insulin secretion results in enhanced metabolism of lipids from the adipose tissue to the plasma. [56] Increased production of very low density lipoprotein [LDL] by the liver results from increased delivery of fatty acids because of decreased utilization by muscle and increased delivery of fatty acids from visceral abdominal fat to the liver via the portal circulation. Decreased catabolism of postprandial triglyceride rich lipoprotein particles because of reduced lipoprotein lipase activity accentuates diabetic dyslipidemia. [57] The levels of serum lipids are usually elevated in diabetes mellitus and such an elevation represents the risk factor for coronary heart diseases. [58-59] The reduction of serum lipids concentration through dietary or drug therapy seems to be associated with a decrease in the risk of vascular diseases. [60]

In the present study, administration of the vehicle to alloxan induced diabetic rats resulted in a gradual increase in the level of TC, TG, LDL and gradual decrease in HDL at 21 days of study. In contrast to this, continuous administration of both extracts of *Garcinia indica* [500 mg/kg] in the diabetic rats, levels of TC, TG, and LDL were decreased significantly ($P < 0.01$) while the value of HDL was increased significantly ($P < 0.01$) [Table 2]. Present study reports that the AEGI and EEGI effectively decrease the fasting blood glucose level in alloxan induced diabetic rats.

Blood urea and creatinine

Kidney maintains optimum chemical composition of body fluids by acidification of urine and removal of metabolite waste such as urea, uric acid, creatinine and ions. [61] During renal disease, the concentration of these metabolites increased in the blood. In this study the levels of urea and creatinine were increased thus indicating presence of significant kidney damage.

Aqueous and ethanol extract of *Garcinia indica* Linn fruit rind at dose 500 mg/kg, *p.o.* indicated that there was gradually decreased in blood urea level at 7th, 14th and 21st day of the treatment. The maximum reduction in blood urea level was achieved on 21st day of the study (Table 3).

Table 1: Effect of daily oral administration of aqueous and ethanolic extract of *Garcinia indica* Linn fruit rind on fasting blood glucose level in diabetic rats for 21 days

Treatment	Dose mg/kg	Post treatment level (Days)			
		0	7	14	21
Vehicle control	10ml	88 ± 2.52	84 ± 5.57	84 ± 3.57	85 ± 3.5
Diabetic control	10ml	770 ± 9.16**	750 ± 7.68**	680 ± 9.78**	655 ± 8.08**
Glucose	10	717 ± 8.00**	269 ± 6.73**	109 ± 3.57**	85 ± 3.15**
AEGL	500	745 ± 9.52**	470 ± 7.04**	181 ± 5.51**	98 ± 3.21**
EEGL	500	750 ± 8.58**	506 ± 8.51**	285 ± 6.51**	146 ± 4.58**

Values are expressed as mean ± S.E.M.; One way analysis of variance [ANOVA- Dunnett test]; ** $p < 0.01$ when compared with diabetic control and when diabetic control compared with vehicle control.; Glucose, Glibenclamide [standard drug]; AEGL, aqueous extract of *Garcinia indica* fruit rinds; EEGL, ethanol extract of *Garcinia indica* fruit rinds

Table 2: Effect of daily oral administration of aqueous and ethanol extract of *Garcinia indica* Linn fruit rind on serum lipid profile in diabetic rats for 21 days

Treatment	Dose mg/kg	Post treatment levels (Days)			
		0	7	14	21
Total cholesterol (mg/dl)					
Vehicle control	10 ml	126 ± 2.15	120 ± 2.52	122 ± 3.05	120 ± 1.80
Diabetic control	10 ml	170 ± 4.30**	175 ± 4.08**	179 ± 5.73**	180 ± 6.00**
Glb	10	184 ± 5.52**	141 ± 3.30**	128 ± 5.57**	115 ± 4.08**
AEGI	500	168 ± 5.00**	146 ± 5.64**	132 ± 3.08**	118 ± 3.15**
EEGI	500	170 ± 4.30**	155 ± 4.08**	145 ± 3.15**	131 ± 4.05**
HDL cholesterol (mg/dl)					
Vehicle control	10 ml	38 ± 2.27	39 ± 3.93	39 ± 3.10	40 ± 3.58
Diabetic control	10 ml	27 ± 2.29**	21 ± 3.58**	16 ± 2.03**	12 ± 2.91**
Glb	10	23 ± 2.94**	35 ± 3.07**	42 ± 4.04**	45 ± 3.58**
AEGI	500	22 ± 1.78**	32 ± 2.95**	39 ± 3.19**	43 ± 3.82**
EEGI	500	21 ± 2.22**	29 ± 3.77**	36 ± 2.91**	41 ± 3.94**
Triglyceride (mg/dl)					
Vehicle control	10 ml	84 ± 4.65	99 ± 3.70	88 ± 3.70	90 ± 5.76
Diabetic control	10 ml	224 ± 7.15**	216 ± 5.95**	208 ± 5.35**	205 ± 7.61**
Glb	10	204 ± 7.61**	150 ± 4.56**	110 ± 6.67**	75 ± 6.22**
AEGI	500	210 ± 8.53**	164 ± 5.68**	125 ± 6.78**	82 ± 4.67**
EEGI	500	215 ± 6.98**	178 ± 5.33**	136 ± 4.32**	89 ± 3.64**
LDL cholesterol (mg/dl)					
Vehicle control	10ml	71±3.67	61.2±4.77	65.4±4.0	62±3.45
Diabetic control	10ml	98±4.56**	110.8±7.2**	121.4±5.60**	127±6.5**
Glb	10	120.2±4.78**	76±6.44**	64±5.45**	55±3.5**
AEGI	500	104±5.13**	81.2±5.67**	68±3.37**	58.6±3.44**
EEGI	500	106±7.45**	90.4±5.89**	81.8±5.23**	72.2±5.55**

Values are expressed as mean ± S.E.M.; One way analysis of variance [ANOVA- Dunnett test]; ** $p < 0.01$ when compared with diabetic control and when diabetic control compared with vehicle control.; HDL, high density lipoprotein; LDL, low density lipoproteins; Glucose, Glibenclamide [standard drug]; AEGL, aqueous extract of *Garcinia indica* fruit rinds; EEGL, ethanol extract of *Garcinia indica* fruit rinds

Table 3: Effect of oral administration of aqueous and ethanol extract of *Garcinia indica* Linn fruit rind on serum urea and creatinine levels in diabetic rats for 21 days

		Post treatment levels [Days]			
Treatment	Dose mg/kg	0	7	14	21
Serum urea (mg/dl)					
Vehicle control	10 ml	24 ± 0.91	25 ± 0.82	26 ± 0.36	28 ± 1.25
Diabetic control	10 ml	62 ± 2.29**	88 ± 2.98**	90 ± 3.58**	99 ± 1.69**
Glucose	10	54 ± 1.09**	43 ± 1.36**	40 ± 2.58**	33 ± 3.58**
AEGL	500	58 ± 2.91**	50 ± 5.36**	45 ± 2.65**	40 ± 4.36**
EEGL	500	62 ± 1.66**	56 ± 5.78**	50 ± 5.6**	45 ± 2.6**
Serum creatinine (mg/dl)					
Vehicle control	10 ml	0.7 ± 0.03	0.65 ± 0.01	0.65 ± 0.02	0.65 ± 0.01
Diabetic control	10 ml	1.2 ± 0.02**	1.2 ± 0.03**	1.29 ± 0.07**	1.2 ± 0.05**
Glucose	10	1.0 ± 0.06**	0.85 ± 0.08**	0.8 ± 0.06**	0.74 ± 0.16**
AEGL	500	1.0 ± 0.12**	0.9 ± 0.24**	0.9 ± 0.03**	0.8 ± 0.5**
EEGL	500	1.0 ± 0.06**	0.95 ± 0.08**	0.9 ± 0.06**	0.9 ± 0.07**

Values are expressed as mean ± S.E.M.; One way analysis of variance (ANOVA- Dunnett test); ** $p < 0.01$ when compared with diabetic control and when diabetic control compared with vehicle control.; Glucose, Glibenclamide (standard drug); AEGL, aqueous extract of *Garcinia indica* fruit rinds; EEGL, ethanol extract of *Garcinia indica* fruit rinds

Aqueous and ethanol extract of *Garcinia indica* Linn fruit rind at dose 500 mg/kg, *p.o.* showed reduction in blood creatinine level at 7th day (0.9 mg/dl and 0.95 mg/dl respectively) which were maintained over a period of 21 days.

In present study the aqueous and ethanol extracts of *Garcinia indica* Linn fruit rind showed significant ($P < 0.01$) reduction in fasting blood glucose level, total cholesterol, triglyceride, LDL, urea and creatinine in alloxan induced diabetic rats. *Garcinia indica* Linn fruit rind extracts exhibit inhibition of lipid peroxidation

and free radical scavenging action due to its antioxidant potential that might have been responsible for observed antidiabetic and antihyperlipidemic and renal protective potential.

From this study, we can speculated that aqueous and ethanol extract *Garcinia indica* fruit rind have beneficial effects on blood glucose level as well as improving lipid profile and renal profile due to diabetes mellitus. The present investigation has also opened an avenue for further research especially with reference to the development of potent formulation for diabetes mellitus from *Garcinia indica* Linn fruit rind.

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