

Original Article

Hypoglycemic and hypolipidemic effects of *Garcinia cambogia* extracts in streptozotocin-nicotinamide induced diabetic rat model

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Abstract: Background and objectives: Diabetes mellitus, a global health problem, is associated with metabolic complications such as hyperglycemia, hyperlipidemia, hypertension, cardiovascular diseases, and loss of vision. The present study evaluated the antidiabetic and antihyperlipidemic effects of ethanol extract of *Garcinia cambogia* (L.) N. Robson (*G. cambogia*) fruit rind in a streptozotocin-nicotinamide induced diabetic Wistar Rat model. Materials and Methods: Streptozotocin-nicotinamide was injected intraperitoneally to induce diabetes in Wistar rats. Five groups of rats (n=6) - normal control, diabetic, diabetic treated with *G. cambogia* at 400 mg/kg and 800 mg/kg body weight, and diabetic treated with metformin at 500 mg/kg body weight, were studied. Blood samples were collected after three weeks of treatment. Random blood glucose (RBG), Serum total cholesterol levels (TCL), serum total triglyceride levels (TGL), high-density lipoprotein levels, and body weight were measured. Results: Although *G. cambogia* treatment did not have any antidiabetic activity ($p>0.05$) rind in the streptozotocin-nicotinamide induced diabetic Wistar Rat model, it decreased the serum TCL, and body weight significantly ($P<0.05$). Conclusions: Ethanol extract of *G. cambogia* fruit rind possesses anti-obesity activity and significantly reduces total cholesterol but does not have antidiabetic activity.

Keywords: Animals, *Garcinia cambogia*, diabetes, streptozotocin-nicotinamide, cholesterol

Introduction

Diabetes mellitus (DM) is a group of complex metabolic diseases characterized by hyperglycemia resulting from a defect in insulin secretion and insulin action, or both, that ultimately affects carbohydrate, fat, and protein metabolism. DM is a growing public health concern worldwide [1]. Obesity and overweight are important public health problems as their prevalence rates continue to rise. Worldwide, over 1.9 billion and 650 million adults are reported to be overweight and obese, respectively [2]. Further, >60% live in Asia, mainly in India and China [3]. Obesity increases the risk of developing diseases such as DM, cancers, cardiovascular disease, and musculoskeletal and neuro-

logical disorders [4]. These in turn affect the health of citizens and directly impact the productivity and economy of the country.

Several therapeutic agents are used to treat obesity, diabetes, and hypertension. However, most of these agents pose undesirable side effects such as, lactic acidosis, hyperglycemia, diarrhea, and flatulence, which impose an economic burden [5]. Therefore, extensive research is going on worldwide to find alternative therapeutic strategies to minimize the side effects and cost. The major drug therapy for type II DM comprises insulin secretagogues, biguanides, insulin sensitizers, α -glucosidase inhibitors, incretin mimetics, amylin antagonists, and sodium-glucose co-transporter-2 (SGLT2) inhib-

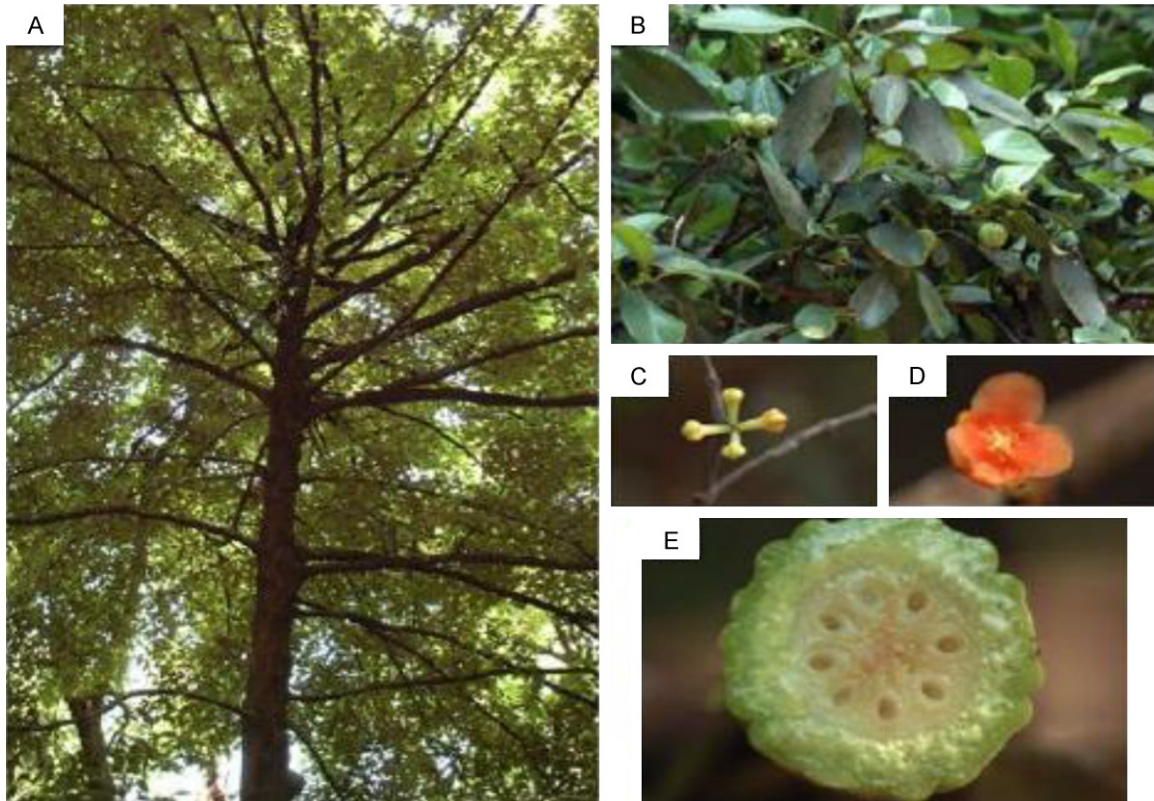


Figure 1. *Garcinia cambogia* tree (A) Shape, (B) Fruiting branch, (C) Flower inflorescence, (D) Male flower, (E) Cross section of the fruit.

itors. Dual drug therapies are often recommended in patients who are unable to achieve therapeutic goals with first-line oral hypoglycaemic agents as monotherapy. Despite the appreciable therapeutic benefits, the conventional dosage forms depict differential bioavailability and short half-life, mandating frequent dosage, and causing greater side effects leading to therapy ineffectiveness and patient non-compliance.

Increasing physical activity, and managing fat and sugar-rich products, are the keys to managing obesity. Indian medicinal plants and their plant products have traditionally been used since ancient times. These plant-based foods have novel protection, and are used as an alternative medicine to treat several medical conditions. Purified and crude extract contains numerous active phytochemicals which exert anti-inflammatory and antioxidant properties by regulating several signaling pathways [6, 7]. The high degree of safety, good effectiveness, wide availability, acceptability, and affordabi-

lity make plant-based therapy a preferable choice.

Garcinia cambogia (L.) N. Robson (*G. cambogia*), belongs to the family Clusiaceae, commonly known as “Malabar Tamarind” is found in the Southeastern regions of the world. This evergreen plant is about 12 meters long and is widely found in the dense forest of Southwest Indian states [8]. The fruit of *Garcinia* can be yellow, orange, or red depending on the ripening condition, and each fruit has 6 or 8 seeds surrounded by a succulent aril (**Figure 1**). The dried rind of the fruit has been used as a food preservative and prevents bacterial infection in fish. The major phytoconstituents in *Garcinia* fruit is hydroxy citric acid (HCA). The intake of *Garcinia* fruit is reported to result in weight loss. Additionally, this plant extract is reported to have several medicinal properties such as anti-inflammatory, anticancer, anti-helminthic, anti-ulcer, antioxidant, and hepatoprotective activities in various *in vivo* and *in vitro* models [8-10].

Hypoglycemic & hypolipidemic effects of *Garcinia cambogia*

Considering the ancient Indian traditional medical system, which used chemical constituents of plants as alternative medicine, the present study aimed to evaluate the anti-hyperglycemic and antihyperlipidemic effects of ethanol extract of *G. cambogia* fruit rind in a streptozotocin (STZ)-nicotinamide (NAD)-induced diabetic Wistar Rat model that mimics type II diabetes mellitus. STZ is known to destroy the insulin-producing pancreatic beta cells, and NAD decreases the damage caused by STZ, thereby resulting in only a partial insulin deficiency similar to that which occurs in type 2 diabetes mellitus.

Materials and methods

Chemicals

Streptozotocin (STZ) and Nicotinamide (NAD) were from Sigma Aldrich, MO, USA, and Metformin drug was obtained from Cipla Pvt. Ltd., India, and all other chemicals used in this project were purchased from Himedia, Mumbai, India.

Preparation *Garcinia* fruit rind ethanol extracts

To prepare crude extract of *G. cambogia*, fresh, mature fruits were collected from a plantation in Kerala, and were identified by Dr. Jayakala Bhandary M. (voucher number 6/10/2016) as *G. cambogia* (L.) N. Robson. The fruit rind was shade dried and then powdered. The powdered rind (1000 gms) of *Garcinia* fruit was loaded into the thimble of Soxhlet apparatus, and ethanol (200 mL) was used as solvent for extraction. Extraction was continued till the exhaustion of constituents. After extraction, the solvent was distilled off by using a rotary flash evaporator. Evaporation of solvent led to a reddish-brown semisolid GC extract, which was dried, weighed, and dissolved in distilled water. Two doses, 400 mg, and 800 mg/kg body weight, were used for treatment. Dose toxicity studies of *G. cambogia* fruits have shown No Observed Adverse Effect Level (NOAEL) of up to 2800 mg/day, suggesting that it is safe for use [11].

Animals

The Institutional Animal Ethical Committee (IAEC) approved the study with reference number IAEC/02/2015/CPCSEA. Guidelines of the Committee for the Purpose of Control and

Supervision of Experiments on Animals (CP-CSEA) were strictly followed for the animal treatment.

Healthy adult Wistar rats of either sex were provided from the local colonies of the Central Animal house facility (Department of Pharmacology). The animals were housed in polypropylene cages with sterile padded husk as beddings and maintained with relative humidity 55±5%, room temperature 25±2°C, and 12/12 h light/dark cycle. Animals were fed with commercial pelleted chow and water *ad libitum* [12]. Animals were acclimatized for one week before the commencement of the study.

Animal model establishment

Diabetes was induced with an intraperitoneal injection of streptozotocin (STZ) at 65 mg/kg body weight. After 15 min, Nicotinamide (NAD) at 110 mg/kg was administered i.p. [13]. Random blood glucose was measured after 72 h of STZ-NAD injections, and only rats with a blood glucose level ≥200 mg/dL were referred to as diabetic animals. STZ was dissolved in citrate buffer (pH 4.5), NAD in normal saline, and metformin was dissolved in distilled water. All sham animals received the vehicle and showed normal glucose levels. Metformin was used as a standard drug, administered orally at a dose of 500 mg/kg body weight [14].

Experimental design

Animals were randomly allocated into five groups with 6 rats in each. All animals were fasted for 12 h (overnight) prior to extract/drug administration. The extracts were suspended in 1 mL of distilled water and were given orally (p.o.), once-a-day, for 21 days, as follows:

Group I (Normal Control), sham animals received normal diet.

Group II (Diabetic Control), diabetic animals with a normal diet.

Group III (Diabetic + GC400), diabetic animals treated with ethanolic extract of *G. cambogia* at a 400 mg/kg body weight dose.

Group IV (Diabetic + GC800), diabetic animals treated with ethanolic extract of *G. cambogia* at an 800 mg/kg body weight dose.

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Group V (Diabetic + metformin), diabetic rats were treated with the standard drug metformin at a dose of 500 mg/kg.

An acute oral toxicity study was done according to Organization for Economic Cooperation and Development (OECD) guidelines No. 423. Each animal was observed individually for any signs of toxicity or death after treatment with the drugs. It was observed once during the first 30 minutes after the first dose, and then periodically during the first 24 h, with special attention given during the first 4 h, and thereafter daily for 14 days. After 14 days, unusual behavioral changes and general physical conditions such as fur observation, eyes, nose, abdomen, external genitals, the occurrence of secretions, and autonomic nervous system activity (e.g., lacrimation, piloerection, respiratory pattern, and response to handling), salivation, diarrhea, lethargy, or sleep were studied in each animal to determine the onset of toxic reactions throughout the experimental period. The body weight of animals was checked at 0, 7, 14, and 21 days.

Blood collection and biochemical assessment

Blood was collected from the tail vein of animals. Random blood glucose (RBG) levels were checked on day 0 (72 h after induction of diabetes with STZ-NAD) and on day 21 using a glucometer (Elegance CT-X10, convergent technologies, Germany). The serum lipid profile was checked only on day 21 using the cardiac puncture method. Enzymatic analysis of serum total cholesterol (TCL) and serum triglyceride (TGL) levels were done by commercially available kits (Accurex Biomedical Pvt. Ltd., Mumbai, India) in an autoanalyzer. High-density lipoproteins (HDL) cholesterol levels were determined by the Trinder CHOD/POD End Point method. Low-density lipoproteins (LDL) cholesterol concentration was estimated using the Friedewald equation [15]. LDL cholesterol = total cholesterol - [TGL/5 + HDL cholesterol]. The cutoff points for TGL, TCL, HDL cholesterol, and LDL cholesterol were ≥ 150 mg/dL, ≥ 200 mg/dL, ≤ 60 mg/dL, and ≥ 130 mg/dL, respectively [16].

Statistical analysis

Experimental data were presented as mean \pm standard deviation for all the values. Comparison between the groups was done with the Student t-test, while the one-way ANOVA fol-

lowed by Tukey's test was done to compare the diabetic group with the remaining test groups; 'p' value < 0.05 was considered significant.

Results

Treatment of animals with ethanolic extract of *G. cambogia* did not show any treatment related signs of toxicity or mortality.

RBG

Group II shows significantly higher RBG levels on both day 0 ($P < 0.001$) and day 21 ($P < 0.05$), as compared to Group I (**Table 1**). There were no significant changes in RBG levels ($P > 0.05$) on day 0 and day 21 of treatment in Group III, Group IV, and Group V as compared to Group II. In Group III and Group IV, although the RBG levels were higher on day 21 as compared to that on day 0, the differences were nonsignificant ($P > 0.05$). However, in Group V, there was a significant reduction in RBG level on day 21 of treatment as compared to day 0 ($P < 0.01$).

Body weight

There was no significant difference in body weight of Group I and Group II between day 0 and day 21 of treatment. However, the body weight was reduced significantly, from day 0 to day 21 of treatment in Groups III ($P < 0.05$), IV ($P < 0.05$), and V ($P < 0.01$).

TCL

There was a significant increase in TCL ($P < 0.001$) of Group II as compared to Group I. There was a significant decrease in TCL of Groups III ($P < 0.01$) and Group IV ($P < 0.001$) as compared to Group II. Although the decrease in TCL seen in Group V was not significant ($P > 0.05$), a significant decrease was seen in TCL of Group III ($P < 0.01$) and IV ($P < 0.001$) as compared to that in Group V.

TGL

There was a significant increase in TGL ($P < 0.01$) of Group II as compared to Group I. There was a nonsignificant decrease in TGL of Group III as compared to that of Group II ($P > 0.05$). However, there was a significant increase in Group III as compared to Group IV ($P < 0.01$) and Group V ($P < 0.001$). Although the TGL in Group V was less than in Group II, the difference was nonsignificant ($P > 0.05$).

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Table 1. Effect of different doses of *Garcinia cambogia* rinds (GC) on blood glucose, cholesterol, triglyceride, high-density lipoprotein levels, and body weight in streptozotocin-nicotinamide induced diabetic rats

Factor Groups	Random blood glucose; mg/dL		Total cholesterol (TCL); mg/dL	Triglyceride (TGL); mg/dL	High density lipoproteins (HDL); mg/dL	Body weight; grams	
	DAY 0	DAY 21	DAY 21	DAY 21	DAY 21	DAY 0	DAY 21
(Group 1) Normal Control	98.33±4.76	112.17±10.79	69.50±13.39	84.83±11.53	42.50±4.80	254.67±52.13	271.67±46.22
(Group 2) Diabetic Control	284±48.85 ^{###}	278.67±137.94 [#]	120.33±31.00 ^{###}	202.33±34.91 ^{##}	34.66±7.97	265.83±68.10	242.66±53.35
(Group 3) Diabetic + GC400	244.83±70.18 [§]	283.33±89.9	38.50±14.63 ^{**,\$\$}	137.33±24.65	39.33±9.438 [§]	261.01±34.82	222.83±12.64 [¥]
(Group 4) Diabetic + GC800	306.33±79.12	348.17±116.88	43.33±13.37 ^{***,\$\$}	312.33±62.27 ^{**,\$\$}	36.83±4.58	305.17±49.73	227.5±42.40 [¥]
(Group 5) Diabetic + metformin	378.83±51.57	276.67±46.63 ^{¥¥}	88.83±15.58	166.33±66.38	26.00±4.147	276±19.71	240.46±13.79 ^{¥¥}

Data expressed as mean ± SD. n=6 (ANOVA and Tukey's test). *P<0.05, **P<0.01 and, ***P<0.001 as compared with normal control groups, **P<0.01 and ***P<0.001 as compared with diabetic controls; §P<0.05, \$\$P<0.01 and, \$\$\$P<0.001 as compared with the metformin group. ¥P<0.05 and ¥¥P<0.01 comparison in day 0 and day 21.

HDL

Further, in Group II, there was a nonsignificant decrease in HDL levels as compared to Group I ($P>0.05$). The HDL levels were higher in Groups III and IV as compared to Group II, but the increase was nonsignificant ($P>0.05$). Group V has the least HDL level as compared to Groups II, III, and IV. The increase in Group III's HDL was significant compared to Group V ($P<0.05$).

Discussion

The aim of the present study was to evaluate the hypoglycemic and hypolipidemic activities of ethanol extract of *G. cambogia* fruit rinds in the streptozotocin-nicotinamide (STZ-NAD) induced diabetic rat model treated with the GC extract orally for 21 days. Although the extracts showed no hypoglycemic effect, it exhibited antiobesity and antilipidemic effects at the tested concentrations.

Hypoglycemic role of *Garcinia*

Although most species of *Garcinia* are known to have an antidiabetic effect, in the present study, both doses, 400 and 800 mg/Kg body weight, of *G. cambogia* fruit rind administered to the diabetic rat model for 21 days (3 weeks) failed to combat the hyperglycemia (RBG). Kirana and Srinivasan (2010), have shown that when aqueous extract of the *G. indica* rind at 100 and 200 mg/Kg body weight is administered for a duration of four weeks, there is a decrease in both fasting and post prandial blood sugar levels in STZ induced diabetic rat models [17]. One of the reasons could be that the duration of treatment was only for 3 weeks as compared to the 4 weeks done by most studies. Further, the NAD injected along with STZ has a protective effect on the insulin-producing beta cells against the action of STZ - which destroys the insulin-producing cells - resulting in only a partial insulin deficiency [18]. This probably explains the nonsignificant changes ($P>0.05$) in the FBG between day 0 and day 21 in groups III and IV. However, Group V treated with metformin showed a significant decrease ($P<0.01$) on day 21 as compared to day 0.

The hypoglycemic or antidiabetic effect of *Garcinia* is attributed to the presence of phytochemicals that inhibit the enzymes α -amylase

and α -glucosidase required for digestion of the dietary carbohydrates. Inhibition of these two core enzymes can prolong the digestion of carbohydrates, followed by their absorption. Flavonoids and phenols are known to inhibit these enzymes. Liu et al., (2013), have reported that the alcoholic plant extract was found to inhibit the activities of α -amylase and α -glucosidase [19]. Chen et al., (2021), in their study with *G. linii*, another *Garcinia* spp, have concluded that some of the chemical compounds from *G. linii* inhibited α -amylase and α -glucosidase better than the clinical drug, which they have confirmed by docking, *in vitro*, and *in vivo* studies. They also proved that there is suppression of intestinal uptake of glucose [20]. In addition, the biological properties of the plant extracts is dependent of the phytochemical composition. The phytochemical composition of plants can vary based on a number of factors such as geographical location, climatic conditions, and type of soil where the plants grow. [21].

Body weight

Garcinia sps. is known to have an antiobesity effect. In the present study, the body weight reduced significantly, from day 0 to day 21 of treatment in Groups III ($P<0.05$), IV ($P<0.05$), and V ($P<0.01$). *G. cambogia* extracts contain hydroxycitric acid (HCA) a competitive inhibitor of ATP citrate lyase [22]. Inhibition of this enzyme effects both carbohydrate and lipid metabolism. Chuah et al. (2013), have listed four different mechanisms for the antiobesity effect of HCA, such as (1) regulation of serotonin, suppression of intake of food, (2) decreased lipogenesis (storage in adipose tissue), (3) increased β oxidation of fatty acids (for energy), and (4) down-regulation of a number of obesity-associated genes [23]. HCA is said to play a crucial role in the hypolipidemic role, i.e., decreasing cholesterol and triglycerides, while it had no effect on the HDL levels [24], which was seen in the present study as well. There was no significant difference in the serum HDL levels of the extract-treated groups as compared to the diabetic controls.

TCL

In the present study, STZ-NAD diabetic rats had significantly higher TCL as compared with both the concentrations of the extract-treated

groups III ($P < 0.01$) and IV ($P < 0.001$). This clearly shows that *G. cambogia* extract used in the present study had a hypocholesterolemic effect. *G. cambogia* is rich in flavonoids. Koshy and Anila, (2001), had earlier reported that the rats - fed normal and cholesterol-containing diets - administered with flavonoids from *G. cambogia*, have significantly lower lipid levels due to an inhibition of the HMG CoA reductase enzyme, which is the regulatory enzyme of cholesterol biosynthesis, and increased excretion of cholesterol degradation products [25].

TGL

At lower concentrations, the *G. cambogia* extract was able to decrease TGL (Group III) as compared to that of Group II, in the present study; but the decrease was not significant ($P > 0.05$). Sarma et al., (2016), have reported a similar hypolipidemic potential of *G. pedunculata* extract, which is rich in polyphenol, in high-fat diet (HFD) rats. As mentioned earlier, the nonsignificant decrease in TGL could be due to the variation in the phytochemical composition of the extract [26].

Conclusions

G. cambogia extract in the present study had antiobesity and hypolipidemic effects but no hypoglycemic effect. This extract could be further explored for weight loss effects.

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Disclosure of conflict of interest

None.

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