EVALUATION OF HYPOLIPIDEMIC ACTIVITY OF FRUIT RIND EXTRACTS OF *GARCINIA GUMMI-GUTTA* IN DIET-INDUCED HYPERLIPIDEMIC RATS

BARATHANE DATCHANAMURTY[1]*, MANIMEKALAI K[2], KARTIK J SALWE[2]

[1]Department of Pharmacology, Vinayaka Missions Medical College, Vinayaka Missions Research Foundation (Deemed to be University), Karaikal, Pondicherry, India. [2]Department of Pharmacology, Mahatma Gandhi Medical College and Research Institute, Sri Balaji Vidyapeeth University, Pondicherry, India. Email: barathane20@gmail.com

ABSTRACT

Objective: The objective of the study was to evaluate the hypolipidemic activity of fruit rind extracts of *Garcinia gummi-gutta* in diet-induced hyperlipidemic rats.

Methods: Hydroalcoholic extract of fruit rinds of *G. gummi-gutta* was prepared using Soxhlet apparatus. 30 Wistar albino rats were divided into five groups (n=6). Except for Group 1, all the other groups were treated with hyperlipidemic diet (HLD) for 4 weeks. After induction, the Groups 3 and 4 were treated with the extracts at 100 mg/kg and 200 mg/kg doses, respectively, whereas Group 5 received the standard drug atorvastatin at 10 mg/kg for the next 4 weeks. Lipid profile was estimated at the end of each week. At the end of the study, rats were sacrificed and the liver and heart were analyzed for histopathological changes. Data expressed as mean±standard error of the mean. Statistical analysis was done using one-way ANOVA followed by *post hoc* Tukey test. p<0.05 considered statistically significant.

Results: The serum levels of total cholesterol (TC), triglycerides (TG), very low-density lipoprotein (VLDL), and LDL were significantly increased and the levels of high-density lipoprotein (HDL) were significantly decreased when compared to normal control. The groups which received *G. gummi-gutta* rind extract at 100 mg/kg and 200 mg/kg showed a significant decrease in the mean cholesterol, TG, LDL, VLDL levels, and an increase in HDL levels when compared to the HLD group. The group which received the extract at higher dose (REGG200) was found better than the lower dose (REGG 100). REGG 200 showed significant improvement in increasing the HDL levels than all the test groups. The standard drug atorvastatin was found better than REGG100 but there was no significant difference between high doses of the extract and atorvastatin.

Conclusion: The fruit rinds extract of *G. gummi-gutta* was able to decrease the elevated serum lipids (TC, TG, LDL, and VLDL) and consequently increase the HDL levels in a dose-dependent manner.

Keywords: *Garcinia gummi-gutta*, Hypolipidemic, Atorvastatin, Lipid profile.

INTRODUCTION

Cardiovascular disease (CVD) was previously assumed to be a problem of developed and industrialized nations, but over the past few decades, it has slowly infiltrated into the low and middle-income countries where it accounts for nearly 30% of all deaths [1]. In India, the prevalence of CVD has grown exponentially and accounts for nearly 24% of all adult deaths [2]. Reports submitted by the National Commission on Macroeconomics and Health have estimated that there would be 62 million patients with coronary artery disease by 2015 and of these 23 million would be people younger than 40 years [3].

The umbrella term CVD has multifactorial etiopathogenesis and its prevalence is attributed to lifestyle changes due to urbanization, stress, lack of physical activity, nutritional transitions, and other metabolic disorders such as diabetes and hypothyroidism.

For decades, dyslipidemia has been identified as an independent modifiable risk closely associated with the incidence of CVD. Furthermore, increased levels of low-density lipoprotein (LDL) with a concurrent decrease in high-density lipoprotein (HDL) contribute to the process of atherogenesis and evolution of atheromatous plaque [4].

Conventional preparations of lipid-lowering drugs such as statins, fibrates, bile acid sequestrants, and niacin are efficient in lowering serum lipids but not always free of side effects [5].

For many years plants and plant products have been identified as a potentially safer alternative to synthetic drugs. Despite such intensive research on various herbal medicines, many species of plants are still left unexplored.

Garcinia gummi-gutta also known as *Garcinia cambogia* is a diminutive purple fruit native to India and Southeast Asia. The fruit rinds find its use as a food preservative, flavoring agent, and carminative [6]. Traditionally, it is used for the treatment of constipation, piles, rheumatism, edema, menstrual abnormalities, and parasitic infestations [7]. Although many of its biological effects have been explored to depth, still satisfactory studies to exploit its hypolipidemic activity have not been conducted. Therefore, the present study was planned to evaluate the hypolipidemic activity of *G. gummi-gutta* fruit extract using animal models.

METHODS

Collection and identification of plant materials
The fruit of *G. gummi-gutta* was collected during the winter season in the month of August from Palode area of Thiruvananthapuram district, Kerala, India, and was authenticated by a local botanist from Science College. The fruit rinds weighing 5 kg were separated along the grooves and deseeded. They were later cleaned, shade dried, pulverized, and stored in airtight containers until the commencement of the extraction process.

Preparation of rind extract

Hydroalcoholic extract was prepared as per the procedure elaborated by Mahanta and Mukherjee [8]. About 40–45 g of dried powder was packed in the thimble of Soxhlet apparatus, and extraction was carried out continuously with 95% ethanol refluxing at 50–70°C which yielded a dark brown sticky mass. The extract was concentrated and dried using a ventilated oven at 45°C for 24 h. The stock powder was stored in a glass desiccator at 4°C. The total yield per cycle was around 15% (~6 g) per cycle.

Chemicals

Pure cholesterol and cholic acid were obtained from Loba Chemie Pvt., Ltd., Mumbai. Atorvastatin (Lipvas) of Cipla Company, Mumbai, was procured from a local medical store. 2-thiobarbituric acid was purchased from Sigma Aldrich, Bengaluru. All other solvents and chemicals used in the study were of analytical grade and purchased from SD fine - chem. Mumbai.

Ethical clearance

Ethical clearance was taken from Institutional Animal Ethics Committee of the institute before the commencement of the study.

Animals

Adult male Wistar albino rats 10–12 weeks of age weighing 180±20 g were procured from King's Institute, Guindy, Chennai. They were housed and maintained in the central animal house of the institute 2 weeks before the commencement of the study so that they could adapt to the new environment. Animals were kept in polypropylene cages with dry paddy husk bedding maintaining a room temperature of 26±2°C and relative humidity of 45–55% with 12:12 h dark and light cycle. They were fed with standard pellet diet and water *ad libitum*. The nutritional value of the standard pellet diet was 21% of protein, 5% of lipids, 4% of crude fiber, 8% of ash, 1% of calcium, 0.6% of phosphorus, 3.4% of glucose, 2% of vitamins, 55% of carbohydrates, and produced energy of 3600 kcal/kg. Care of the animals in the central animal house was strictly in accordance with the guidelines drafted by the Committee for the purpose of Control and Supervision of Experiments on Animals, New Delhi, India.

Acute toxicity testing

A pilot study was performed using two doses 1000 mg/kg body weight and 2000 mg/kg body weight of the fruit rind extract of *G. gummi-gutta*. The doses selected were 10 and 20 times more than the earlier study. The animals were observed continuously for 4 h and then occasionally for further 4 h and finally overnight. Animals were observed for tremors, clonic convulsions, tonic extensions, catatonia, spasticity, opisthotonus, ataxia, sedation, ptosis, and respiration. The animals were continuously observed for 24 and 72 h for any lethality or death.

Dose selection

As the limit dose did not exhibit any signs of toxicity, a dose of 200 and 100 mg/kg, p.o., which was 1/10th and 1/20th of 2000 mg/kg, was taken up for the main study. Atorvastatin at a dose of 10 mg/kg was taken as standard control.

Hyperlipidemic diet (HLD)

Method of Blank with modification was used to produce diet-induced hyperlipidemia. HLD was prepared daily by mixing standard pellet diet (92%), cholesterol (2%), cholic acid (1%), and coconut oil (5%) and was molded into pellets [9].

Experimental design

A total of 30 healthy adult Wistar albino rats were used in the study. The total duration of the study was 8 weeks. Following acclimatization for 1 week, a baseline measurement of lipid profile was performed for all the rats. In an attempt to eliminate bias, the rats were numbered and grouped based on random numbers generated using computer software.

Induction of hyperlipidemia

The study consists of five groups with six rats in each group (n=6). Except for Group 1 which received standard pellet diet and water *ad libitum*, all the remaining four groups received HLD for a period of 30 days.

On day 30, the lipid profile of the rats in all the four groups was estimated and induction of hyperlipidemia was confirmed.

Following successful induction, the rats belonging to those four groups were treated with the extracts, and the standard drug between 9 and 10 am daily for another 30 days suspended in 1% carboxymethylcellulose and administered using a steel gavage needle (Table 1).

Estimation of lipid profile

Blood samples for the estimation of lipid profile were taken from the lateral tail vein as per method elaborated by Diehl *et al.* [10]. Blood samples were collected on day 0 (baseline) and thereafter on 30th, 45th, and 60th day. Serum was separated by centrifugation at 3000 rpm for 10 min. It was then kept frozen at −20°C until analysis. Total cholesterol (TC) level was calculated by the enzymatic method and expressed in mg/dl. HDL levels were calculated using polyanion precipitation and expressed as mg/dl. LDL cholesterol level was calculated using Friedewald's equation and expressed in mg/dl. Triglycerides (TG) in serum were converted to glycerol and then estimated using glycerol kinase enzyme based kinetic method and expressed in mg/dl. Very LDL is calculated using the formula:

$$VLDL = \frac{TG}{5}$$

At the end of 8 weeks, all the rats were sacrificed by an overdose of sodium pentobarbital 150 mg/kg i.p. Heart and liver were dissected and washed with the physiological salt solution and fixed with 10% formalin.

Thiobarbituric acid reactive substances (TBARS) assay

About 1 ml of serum was mixed with 500 μl of 15% trichloroacetic acid in 0.25 N hydrochloric acid (HCl) and 500 μl of 0.375% thiobarbituric acid in 0.25 N HCl. This was shaken well to mix thoroughly and was then heated in a boiling water bath at 95°C for 15 min. After bringing it down to room temperature, it was centrifuged at 1000 r.p.m for 10 min and the reddish-pink supernatant was collected. Absorbance was determined using Labman double beam UV-visible spectrophotometer (LMSP-UV1900) tuned to a wavelength (λ) at 535 nm against a blank that contained all the reagents minus the serum [11]. The concentration of malondialdehyde (MDA) in the serum was calculated using molar extinction coefficient 1.56 M/cm, and the results were expressed in ηmol/ml of plasma [12].

Histopathology

The liver and heart fixed in 10% formalin were washed, dehydrated in descending grades of isopropanol and finally rinsed with xylene. The tissues were then embedded in molten paraffin wax. Sections were cut using a microtome at a thickness of 5 μm and then stained with

Table 1: Experimental design

Group	Purpose	Treatment
Group 1	Normal control	Standard pellet diet+1% CMC
Group 2	HLD control	HLD+1% CMC
Group 3	REGG 100	HLD+rind extract of *G. gummi-gutta* at 100 mg/kg
Group 4	REGG 200	HLD+rind extract of *G. gummi-gutta* at 200 mg/kg
Group 5	Standard group	HLD+Atorvastatin at 10 mg/kg

HLD: Hyperlipidemic diet, REGG100: Rind extract of *Garcinia gummi-gutta* at 100 mg/kg, REGG200: Rind extract of *Garcinia gummi-gutta* at 200 mg/kg, *G. gummi-gutta: Garcinia gummi-gutta*, CMC: Carboxymethylcellulose

hematoxylin and eosin [13]. The sections were observed under light microscope at a magnification of ×10 (Adeltavision Trinocular Digital Microscope) for histopathological changes.

Statistical analysis

Collected data were entered in Microsoft Excel 2013 and analyzed using SPSS statistical software version 17. Results were expressed in mean±standard error of the mean as tables. Statistical analysis was performed using one way ANOVA followed by *post hoc* Tukey's test. The $p < 0.05$ was considered statistically significant at 95% confidence interval.

RESULTS

Acute toxicity study of REGG in rats

Acute toxicity studies confirmed that the fruit rind extract of *G. gummigutta* up to a dose of 2000 mg/kg body weight was non-toxic. No death was observed for up to 72 h. There was no lethality or any toxic reactions found at any of the doses selected until the end of the study.

Effect of the rind extract of *G. gummi-gutta* on serum lipid levels

The serum levels of TC, TG, VLDL, and LDL were significantly increased, and the levels of HDL were significantly decreased when compared to normal control.

The groups which received *G. gummi-gutta* rind extract at 100 mg/kg and 200 mg/kg showed a significant decrease in the mean cholesterol, TG, LDL, VLDL levels, and an increase in HDL levels when compared to the HLD group. The group which received the extract at higher dose (REGG200) was found better than the lower dose (REGG 100). REGG 200 showed significant improvement in increasing the HDL levels than all the test groups.

The standard drug atorvastatin was found better than REGG100, but there was no significant difference between a high dose of *G. gummi-gutta* rind extract and atorvastatin. REGG 200 mg/kg showed a marginal increase in HDL levels than the standard drug (Tables 2-6).

Effect of the rind extract of *G. gummi-gutta* on TBARS levels

Serum TBARS levels were significantly higher (3.42±0.04 ηmol/ml) in rats treated with HLD. Hyperlipidemia significantly increased lipid peroxidation with the generation of reactive oxygen species due to decreased innate antioxidant activity. The groups treated with the standard drug atorvastatin and the groups treated with REGG at both doses showed a significant decrease in TBARS levels ($p < 0.001$) when compared to HLD control. The concentration of MDA in REGG 200 (1.03±0.01 ηmol/ml) was significantly lower when compared with other groups (Fig. 1).

Table 2: Effect of fruit rind extract of *Garcinia gummi-gutta* on total cholesterol levels

Groups (n=6)	Total cholesterol levels (mg/dl)			
	Induction of hyperlipidemia		Drug administration	
	Day 0 baseline	Day 30	Day 45	Day 60
Group 1: Normal control	62.67±1.50	61.67±1.73	64.50±1.38	65.50±0.81
Group 2: HLD control	64.00±0.97	128.83±1.08	135.67±0.84##	141.33±1.23
Group 3: REGG 100	65.33±0.71	131.83±1.17	127.50±0.76**,##	109.17±1.30**,##
Group 4: REGG 200	64.17±1.17	129.33±0.49	113.17±0.91**,##	99.33±1.26**,##
Group 5: Standard control	65.83±1.66	129.00±1.18	106.00±0.97**	93.67±0.80**

Data expressed as mean±SEM. n=6 in each group. Significance at *$p < 0.05$, **$p < 0.001$ as compared to HLD control, #$p < 0.05$, ##$p < 0.001$ as compared to standard control. HLD: Hyperlipidemic diet, REGG 100 and REGG 200: Rind extract of *Garcinia gummi-gutta* at 100 mg/kg and 200 mg/kg, Standard control: Atorvastatin 10 mg/kg, SEM: Standard error of mean

Table 3: Effect of fruit rind extract of *Garcinia gummi-*gutta on triglyceride levels

Groups (n=6)	Triglyceride levels (mg/dl)			
	Induction of hyperlipidemia		Drug administration	
	Day 0 baseline	Day 30	Day 45	Day 60
Group 1: Normal control	79.83±1.25	79.67±1.28	80.50±0.96	82.33±1.09
Group 2: HLD control	83.83±0.87	182.50±1.18	197.83±2.95##	204.00±3.22
Group 3: REGG 100	81.67±0.88	181.50±1.12	165.17±1.47**,##	148.50±1.77**,##
Group 4: REGG 200	81.17±1.08	179.83±1.30	143.33±1.45**,##	115.33±1.26**,##
Group 5: Standard control	83.50±0.76	180.50±0.76	120.17±1.30**,##	106.17±1.28**

Data expressed as mean±SEM. n=6 in each group. Significance at *$p < 0.05$, **$p < 0.001$ as compared to HLD control. #$p < 0.05$, ##$p < 0.001$ as compared to standard control. HLD: Hyperlipidemic diet, REGG 100 and REGG 200: Rind extract of *Garcinia gummi-gutta* at 100 mg/kg and 200 mg/kg, Standard control: Atorvastatin 10 mg/kg, SEM: Standard error of mean

Table 4: Effect of fruit rind extract of *Garcinia gummi-gutta* on low-density lipoprotein cholesterol levels

Groups (n=6)	LDL levels (mg/dl)			
	Induction of hyperlipidemia		Drug administration	
	Day 0 baseline	Day 30	Day 45	Day 60
Group 1: Normal control	18.53±2.06	17.57±1.98	19.90±1.45	19.03±0.86
Group 2: HLD control	22.23±1.17	63.83±2.17	72.27±0.31##	75.70±1.41
Group 3: REGG 100	22.17±1.31	66.53±1.74	60.97±0.76**,##	43.30±1.79**,##
Group 4: REGG 200	21.77±1.04	65.87±1.59	46.50±0.85**,##	31.10±1.85**
Group 5: Standard control	23.13±1.67	62.90±1.77	40.30±0.95**	30.27±1.61**

Data expressed as mean±SEM. n=6 in each group. Significance at *$p < 0.05$, **$p < 0.001$ as compared to HLD control. #$p < 0.05$, ##$p < 0.001$ as compared to standard control. HLD: Hyperlipidemic diet, REGG 100 and REGG 200: Rind extract of *Garcinia gummi-gutta* at 100 mg/kg and 200 mg/kg, Standard control: Atorvastatin 10 mg/kg, LDL: Low-density lipoprotein cholesterol, SEM: Standard error of mean

Table: 5: Effect of fruit rind extract of *Garcinia gummi-gutta* on VLDL cholesterol levels

Groups (n=6)	VLDL levels (mg/dl)			
	Induction of hyperlipidemia		Drug administration	
	Day 0 baseline	Day 30	Day 45	Day 60
Group 1: Normal control	15.97±0.25	15.93±0.26	16.10±0.19	16.47±0.22
Group 2: HLD control	16.77±0.17	36.50±0.24	39.57±0.59##	40.80±0.64##
Group 3: REGG 100	16.33±0.18	36.30±0.22	33.03±0.29**,##	29.70±0.35**,##
Group 4: REGG 200	16.23±0.22	35.97±0.26	28.67±0.29**,##	23.07±0.25**,#
Group 5: Standard control	16.70±0.15	36.10±0.15	24.03±0.26**	21.23±0.26**

Data expressed as mean±SEM. n=6 in each group. Significance at *p<0.05, **p<0.001 as compared to HLD control, #p<0.05, ##p<0.001 as compared to standard control.
HLD: Hyperlipidemic diet, REGG 100 and REGG 200: Rind extract of *Garcinia gummi-gutta* at 100 mg/kg and 200 mg/kg, Standard control: Atorvastatin 10 mg/kg,
VLDL: Very low-density lipoprotein cholesterol, SEM: Standard error of mean

Table 6: Effect of fruit rind extract of *Garcinia gummi-gutta* on high-density lipoprotein cholesterol levels

Groups (n=6)	HDL levels (mg/dl)			
	Induction of hyperlipidemia		Drug administration	
	Day 0 baseline	Day 30	Day 45	Day 60
Group 1: Normal control	28.17±0.87	28.17±0.54	28.50±0.76	30.00±0.63
Group 2: HLD control	25.00±0.58	27.00±1.26	23.83±1.08##	24.83±1.72
Group 3: REGG 100	26.83±1.01	29.00±0.86	33.50±0.67**,##	36.17±0.98**,#
Group 4: REGG 200	26.17±1.17	27.50±1.48	37.83±1.25**,##	45.17±1.30**
Group 5: Standard control	26.00±0.86	30.00±1.13	41.67±0.88**	42.17±1.22**

Data expressed as mean±SEM. n=6 in each group. Significance at *p<0.05,**p<0.001 as compared to HLD control, #p<0.05, ##p<0.001 as compared to standard control.
HLD: Hyperlipidemic diet, REGG 100 and REGG 200: Rind extract of *Garcinia gummi-gutta* at 100 mg/kg and 200 mg/kg, Standard control: Atorvastatin 10 mg/kg,
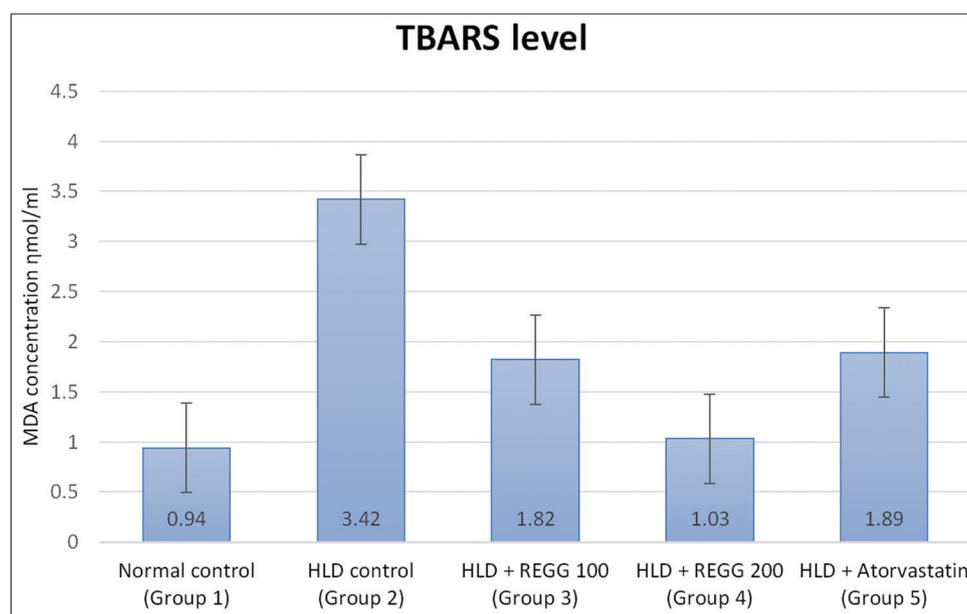HDL: High-density lipoprotein cholesterol, SEM: Standard error of mean

Fig. 1: Effect of fruit rinds of *Garcinia gummi-gutta* on thiobarbituric acid reactive substances levels. Values expressed in ηmol/ml. n=6 in each group. HLD - hyperlipidemic diet, REGG 100 and REGG 200 - rind extract of *G. gummi-gutta* at 100 mg/kg and 200 mg/kg

Effect of the rind extract of *G. gummi-gutta* on liver histopathology
Histology of liver section of normal control exhibited normal hepatic cells each with well defined cytoplasm, prominent nucleus, and nucleolus with well defined central vein and sinusoids (Fig 2a). Rats which received HLD showed micro fatty deposits in the hepatocytes, congestion with mild distortion of the architecture, and early feathery degeneration (Fig. 2b). Hyperlipidemic rats which received REGG 100 showed mild cytoplasmic fatty deposits and periportal leucocyte infiltration (Fig. 2c), whereas hyperlipidemic rats which received REGG 200 showed mild periportal inflammation with infiltration of lymphocytes with well-preserved liver architecture (Fig. 2d). Histopathology of rats treated with HLD along with atorvastatin showed only mild sinusoidal congestion with overall preservation of normal hepatic architecture (Fig. 2e).

Effect of the rind extract of *G. gummi-gutta* on myocardial histopathology
Histopathological sections of the heart did not show significant changes. Fig. 3a shows normal histology of myocardial cells. Oval-elongated nucleus centrally surrounded with homogenous cytoplasm.
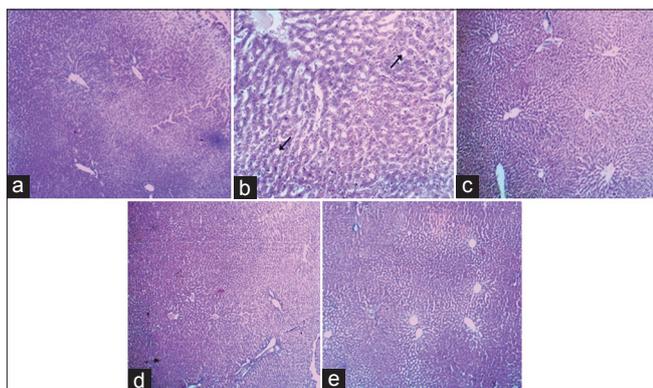
Fig. 2: Effect of the rind extract of *Garcinia gummi-gutta* on liver histopathology. Microphotograph of (a) normal liver, (b) hyperlipidemic diet, (c) REGG at 100 mg/kg, (D) REGG at 200 mg/kg, (e) standard control
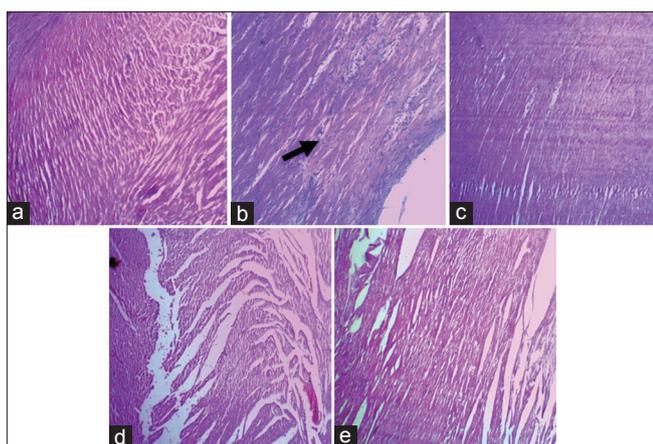

Fig. 3: Effect of the rind extract of *Garcinia gummi-gutta* on myocardial histopathology. Microphotograph of (a) normal myocardium, (b) hyperlipidemic diet, (c) REGG at 100 mg/kg, (d) REGG at 200 mg/kg, (e) standard control

Mild congestion with inflammatory infiltrates was seen with rats which received HLD (Fig. 3b). Hyperlipidemic rats which received the extracts at both doses and the standard control group failed to produce significant changes preserving the overall myocardial integrity (Fig. 3c-e).

The extract at both doses not only halted the inflammatory process but was also able to reverse the condition. This provides conclusive evidence of the hepatoprotective and cardioprotective property of the extract.

DISCUSSION

In the present study, the hypolipidemic activity of fruit rind extract of *G. gummi-gutta* was investigated in diet-induced hyperlipidemic rat models.

The 8-week study was conducted in the Department of Pharmacology in collaboration with the Department of Pathology and Biochemistry in Mahatma Gandhi Medical College and Research Institute, Puducherry.

In our study, supplementation of fruit rind extract at two doses, that is, 100 and 200 mg/kg, produced a dose-dependent reduction in the serum lipids along with significant reduction in lipid peroxidation.

In spite of daily HLD feeding, by the end of day 60, there was a significant reduction of TC, TG, and VLDL in Group 3 with REGG administered at a lower dose (100 mg/kg). When given at a higher dose (200 mg/kg) Group 4 exhibited a marked reduction in TC, TG, and VLDL as compared

to Group 2 and significant reduction as compared with the standard drug atorvastatin.

The results suggest that REGG at both doses reduced the *de novo* cholesterol biosynthesis and favored the redistribution of cholesterol among the lipoprotein molecules. This activity can be attributed to the presence of hydroxycitric acid (HCA) in the extracts which competitively inhibits ATP citrate lyase, the enzyme responsible for the extramitochondrial degradation of citrate to oxaloacetate and acetyl CoA, thus limiting the availability of two carbon units required for fatty acid and cholesterol biosynthesis [6,14,15]. In addition to the above mechanism, HCA initiates gluconeogenesis by converting excess blood lipids to glycogen. It also inhibits pancreatic alpha-amylase and intestinal glucosidase diminishing intestinal carbohydrate absorption [16], and exhibits partial inhibition of HMG-CoA reductase, the key enzyme in cholesterologenesis [17].

In our study, treatment with REGG led to a significant elevation of plasma HDL-cholesterol (HDL-CH) in spite of daily HLD feed. A proportionate increase in HDL levels was observed at the end of 6 weeks with the extracts given at both doses. However, by the end of 8 weeks, the levels of HDL in Group 4 showed significant increase than the standard drug.

Of late, the crucial risk factor for CVD has been identified to be a low level of HDL-CH. Decreased levels of HDL-CH play a direct role in the atherogenesis, and therapeutic interventions promoting HDL-CH levels is widely encouraged. HDL by counteracting LDL oxidation prevents atherogenesis and, recent studies suggest that HDL promotes the reverse cholesterol transport pathway, by inducing an efflux of excess accumulated cellular cholesterol and prevents the generation of oxidized-LDL [18]. Furthermore, HDL not only inhibits the oxidation of LDL but also prevents the 12-lipoxygenase-mediated formation of lipid hydroperoxides [19]. Based on this, our results clearly suggest that fruit rind extract of *G. gummi-gutta* may probably exert their antiatherogenic role, partly by the inhibition of lipids oxidation (evident by reduction in the TBARS levels), and partly by the elevation of HDL-C.

For ages, LDL-CH has been identified as a potential target in CVD risk reduction therapy. Elevated LDL levels augmented with oxidative stress increase the risk of atherosclerosis and CVD [20]. In our study, significant reduction in LDL levels was observed with REGG administered at both the doses. However, values obtained were comparable to that of the standard control following administration of the extracts at higher doses. The biocompound HCA may probably be responsible for the reduction in LDL levels [21].

Most of the findings, in our study, were inconsistent with previous works conducted by Mahendran and Devi who in his study observed that the rind extract of *G. cambogia* at 1000 mg/kg/day for 8 days showed notable hypolipidemic activity on dexamethasone-induced hyperlipidemic rats. He also found that the extract was capable of normalizing increased levels of cholesterol and TG as well as free fatty acid following dexamethasone administration [22]. Similar to the above study, Ramos *et al.* observed that supplementation of the active principle HCA significantly increased HDL-C levels with a decrease in LDL levels [21]. Preuss *et al.* showed that HCA salt at 4.7 g/day in moderately obese subjects was capable of reducing food intake, TC, TG, and LDL levels while significantly increasing the levels of HDL and urinary excretion of fat metabolites [23]. Koshy *et al.* concluded that the flavonoid-rich rind extract exhibited hypolipidemic effect probably by lowering lipid turnover and increased metabolism [24].

The observation done by Leonhardt *et al.* was contradicting with our study findings, which showed supplementation of 3% HCA did not result in decreased cholesterol levels [25]. Brandt *et al.* (2006) noted HCA (1.8%) supplementation for 4 weeks resulted in an unexpected increase in liver lipid and postprandial cholesterolemia [26]. This may be due to an insufficient dose of HCA, which has failed to lower the serum lipids levels.

Oxidative stress induced by HLD is associated with peroxidation of both cellular and circulating lipids which results in the formation of MDA. Quantifying this MDA will positively reflect the severity of an ongoing oxidative damage treatment with fruit rind extract of *G. gummi-gutta* significantly reduced the TBARS level in a dose-dependent manner. The increase in the MDA which is indicative of ongoing oxidative damage was due to oxidative stress induced by HLD [27]. In our study, a significant reduction in TBARS values was observed following treatment with the extract, wherein the maximum reduction was evident with a higher dose of the extract. Thus, it is evident that the rind extract possesses antioxidant properties at both doses, wherein the extract at higher dose exhibited strong antioxidant action compared to other groups. Our study findings were consistent with previous studies conducted by Kolodziejczyk *et al.* who in his study concluded that polyisoprenylated benzophenones such as garcinol and guttiferone K effectively reduced lipid peroxidation of LDL residues (reduced TBARS values), thereby indirectly counteracting oxidative stress in hyperlipidemia [28].

In our study, most of the histopathological findings were consistent with the obtained biochemical parameters. The fruit rind extract at both doses significantly reduced micro fatty deposits, periportal leukocytic infiltration, and disrupted architecture with higher doses showing evidence of hepatocellular recovery. REGG groups at both doses failed to show significant pathological changes in the myocardial cells. This may be due to the fact that hyperlipidemia primarily involves the vascular system and myocardial involvement in hyperlipidemia may be a late phenomenon. In our study, the fruit rind extracts at both the doses have effectively protected the myocardial cells from even the minor toxic insults of lipid peroxidation (signs of inflammation and fatty degeneration).

CONCLUSION

The present study demonstrated the hypolipidemic activity of *G. gummi-gutta*. The fruit rind extract at both doses was able to decrease the elevated serum lipids (TC, TG, LDL, and VLDL) and increase the HDL levels in a dose-dependent manner in spite of daily administration of HLD.

This reduction in lipid profile and TBARS may be probably due to the presence of HCA and other antioxidants in the extracts. Hence, further studies are warranted both in animals and humans before recommending for the clinical use in humans in the prevention and treatment of hyperlipidemia.

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AUTHORS' CONTRIBUTIONS

Dr. Barathane - conceptualized the study, compiled full literature search, and drafted the manuscript. Dr. Kartik. J Salwe - developed standards and edited the manuscript. Dr. Manimekalai - supervisor for the research work and provided guidance for the preparation of this article.

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CONFLICTS OF INTEREST

Nil.

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