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Research Article

Hypolipidemic Activity of *Hiptage benghlensis* Leaf Extracts on High-fat Diet-induced Hyperlipidaemic Rats

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ABSTRACT

The present study was designed to evaluate the hypolipidemic effects of aqueous extract (HBAE) and ethanolic extract (HBEE) of *Hiptage benghalensis* leaves using a high-fat-diet induced hyperlipidemic animal model. Albino male wistar rats (120–150 g) were split into various groups, each of which had six individuals. Normal rats (group I) were received 0.3% carboxy methyl cellulose (CMC) with a standard laboratory diet, while hyperlipidemic rats (group II, III, IV, V, VI and VII) were fed high-fat diet for induction of hyperlipidemia. Hyperlipidaemic control group (group II) received 0.3% CMC (10 mL/kg/day), standard group (group III) received gemfibrozil (50 mg/kg/day, p.o.), HBAE groups (group IV and V) received aqueous extract of *H. benghalensis* (100 and 200 mg/kg/day, p.o.), and HBEE groups (group VI and VII) received an ethanolic extract of *H. benghalensis* (100 and 200 mg/kg/day, p.o.), concurrent with high fat diet for consecutive four weeks. The HBAE and HBEE treatments led to a significant ($p < 0.05$) reduction in serum lipids (TC, TG, LDL and VLDL) and elevation in cardioprotective HDL, when compared to hyperlipidaemic rats (group II). Phytochemical screening revealed the presence of phytoconstituents such as alkaloids, flavonoids, saponins, tannins, phenolic compounds and steroids, which may be attributed to observed hypolipidemic effects. The present study's findings concluded that HBEE (200 mg/kg, p.o.) had potent hypolipidemic effects.

Introduction

Hyperlipidaemia is a lipid metabolism disorder in which there is an increased level of total cholesterol (TC) and/or triglycerides (TG). In addition, there is an increased level of low-density lipoproteins (LDL) along with decreased high-density lipoproteins (HDL) in plasma.[1] It is established that hyperlipidemia especially elevated LDL and decreased HDL is a major risk factor for cardiovascular diseases and atherosclerosis.[2] And CVD is one of the major causes of death worldwide[1]. Reducing the level of cholesterol and triglycerides in plasma is an effective method to treat hyperlipidemia and atherosclerosis. For this reason, a way to prevent and control hyperlipidaemia and related cardiovascular diseases needs to be found. Most synthetic drugs such as statins, fibrates, and others have a promising effect but also have potential side effects such as diarrhea, myositis, abnormal lipid function, and great drug dependence,[3-5] so current research is increasing focus on an alternative natural product that potentially reduces the plasma lipids level with lesser or no side effects than synthetic compounds.

Hiptage benghalensis (L) Kurz, syn. *Hiptage madablota* Geartn. (Family- Malpighiaceae) is commonly known as madhavi, vasantduti, and madhalata in different regions. It is native to India, Southeast Asia, Australia, and the Philippines. It is distributed all over India from the warmer parts of Maharashtra, Karnataka, Madhya Pradesh, and Chhattisgarh. Various plant parts such as leaves, bark, and kernel of seeds are used in the traditional system of medicine for different diseases such as obesity, cough,

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burning sensation, thirst and inflammation, chronic rheumatism, asthma, cancer, and skin diseases.[6-8] The plant contains many active constituents such as tannins, phenolic compounds, flavonoids, saponins, and β-sitosterol.[8, 9] These active constituents have the potential to reduce plasma lipids.[10-12] In this perspective, we assessed the hypolipidemic effects of *H. benghalensis* on high-fat diet-induced hyperlipidaemic rats.

Materials and Methods

Plant Material

H. benghalensis fresh leaves were collected in September from Agriculture Colleges located at Bilaspur, Chhattisgarh region. The National Institute of Science Communication and Information Resources, New Delhi, India (Ref.-NISCAIR/RMHD/Consult/2011-12/1812/112) authenticated the plant.

Drugs and Chemicals

Cholesterol (Central Drug House P. Ltd, New Delhi), Gemfibrozil (Lopid, Pfizer), plasma TC, TG, HDL, and glucose kits (Span Diagnostics Ltd. and Agappe Diagnostic Ltd.) were used in this study. All Chemicals used were of analytical grade.

Extraction

Leaves of *H. benghalensis* were shaded and dried at room temperature. The shaded dried plant material was coarsely powdered through a hand grinder. Coarsely powdered leaves of *H. benghalensis* were extracted with 90% ethanol and water. Ethanolic extract (HBEE) was prepared by a hot continuous extraction process by isolation and aqueous extracts (HBAE) were prepared by cold aqueous percolation method.[13] The extracts were concentrated in a water bath at 40°C and lyophilized at -2°C for further phytochemical and pharmacological evaluations.

Phytochemical Screening

The HBAE and HBEE were qualitatively tested to detect the presence of phytoconstituents. Qualitative tests were carried out by using the methods given by Iqbal *et al.*, 2015.[14]

Animals Used

Albino wistar rats (120–150 g) were used for the present study. The animals were procured from the animal house of Guru Ghasidas Vishwavidyalaya, Bilaspur (Reg. NO. 994/a/GO/06/CPCSEA) and housed under standard environmental conditions according to the guidelines of the Committee for the purpose of Control and Supervision of Experiments on Animals (CPCSEA), (23 ± 2°C, with 55 ± 5% humidity and 12 h light/dark cycle). They were fed a standard laboratory diet (Pranav Agro Industries (P) Ltd., Baroda, Gujarat, India) with water *ad libitium*. The whole experimental protocol was approved by the Institutional Animal Ethical Committee (IAEC) of SLT Institute of Pharmaceutical Sciences, Bilaspur (C.G.) (Ref No.- IAEC/Pharmacy/2012/45) and the experiments were conducted according to ethical principles and guidelines provided by CPCSEA.

Experimental Design

Male wistar rats (120–150 g) were divided into two diet groups, normal rats and hyperlipidaemic rats. Normal rats were fed a standard laboratory diet (SLD) and hyperlipidaemic rats were induced hyperlipidemia by feeding with a high-fat diet (HFD) (Table 1) throughout the experiments. Hyperlipidaemic rats were divided into different groups, each group containing six animals. The experimental groups were treated with their respective drug treatment as mentioned in Table 2 for four weeks.
Body weight gain was examined weakly. Blood samples of animals were collected by a retro-orbital puncture after overnight fasting. Blood was collected in EDTA-containing tubes and allowed to centrifuge at 3000 rpm at 8°C for 15 minutes, and plasma was separated and stored at 8°C until biochemical analysis.

Biochemical Determination

Biochemical parameters, including plasma TC, TG, HDL, and glucose, were estimated using diagnostic kits using the spectrophotometric method. TC was measured by an enzymatic method based on CHOD/PAP.[15] TG was determined by GPO/PAP method.[16] HDL concentration in plasma was determined by the enzymatic method based on specific precipitation of VLDL and LDL in the presence of magnesium ions.[17] Plasma glucose was estimated by GOD/POD method.[18]
LDL was calculated by using Friedwald's (1972) formula[19] and VLDL was calculated as follows:

$$\text{LDL (mg/dL)} = \text{TC} - \text{HDL} - \text{TG}/5$$
$$\text{VLDL} = \text{TG}/5$$

Statistical Analysis

Results were expressed as mean ± standard error of six observations' mean (SEM). The differences between groups were assessed using variance analysis (ANOVA). Differences were considered statistically significant at $p < 0.05$.

Results

Effects of HBAE and HBEE on Body Weight Gain

The results of the effect of oral administration of HBAE and HBEE on body weight gain are presented in Fig. 1. The hyperlipidaemic control group, when compared to the normal control group, showed significant ($p < 0.05$) elevation in average body weight from the second week in a time-dependent manner. Whereas, after four weeks of oral administration of HBAE at 200 mg/kg and HBEE

Table 1: Composition of experimental diets

SLD Ingredients	*Quantity in %*	*HFD Ingredients*	*Quantity in %*
Moisture	8.52	SLD	63
Crude Protein	21.92	Butter	15
Curd Fat	4.36	Ground Nut Oil	10
Crude Fibre	4.30	Cassin	5
Calcium	1.26	Sugar	5
Phosphorus	0.79	Cholesterol	1
Total Ash	6.46	Bile Salt	0.5
Carbohydrates	54.0	Salt Mixture[¥]	0.5

[¥]Salt mixture- NaCl (1 g), KCl (1 g), and $CaCl_2$ (3 g), HFD- High-fat diet, and SLD- Standard Laboratory Diet. Content of SLD was provided by the manufacturer, Pranav Agro Industries (P) Ltd., Baroda, Gujarat, India

Table 2: Experimental groups and their treatments

Group no.	*Groups*	*Treatment (four weeks)*
I	Normal Control	SLD + 0.3% CMC (1 ml)
II	Hyperlipidaemic Control	HFD + 0.3% CMC (1 ml)
III	Standard	HFD + Gemfibrozil (50 mg/kg, p.o.)
IV	HBAE-1	HFD + HBAE (100 mg/kg, p.o.)
V	HBAE-2	HFD + HBAE (200 mg/kg, p.o.)
VI	HBEE-1	HFD + HBEE (100 mg/kg, p.o.)
VII	HBEE-2	HFD + HBEE (200 mg/kg, p.o.)

CMC- carboxy methyl cellulose, HBAE- *Hi. benghalensis* aqueous extract, HBEE- *H. benghalensis* ethanolic extract, HFD- high-fat diet, and SLD- standard laboratory diet.

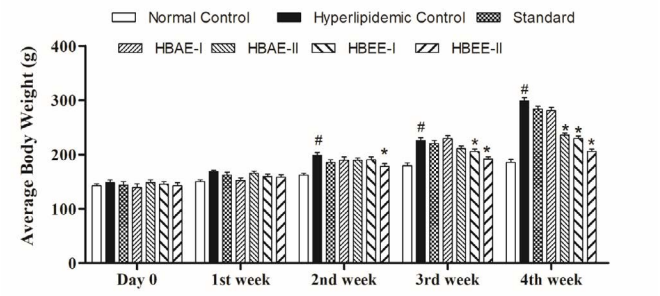

Fig. 1: Effects of HBAE and HBEE on average body weight. Values are expressed as mean ± S.E.M., (n= 6). $^{\#}P < 0.05$ significant values as compared to the normal control group. $^{*}P < 0.05$ significant values as compared to hyperlipidaemic control (two-way ANOVA followed by Bonferroni posthoc test)

at 100 and 200 mg/kg dose levels, when compared to the hyperlipidaemic control group, led to a significant ($p < 0.05$) reduction in average body weight. Moreover, HBAE-I and gemfibrozil, when compared to the hyperlipidaemic control group, showed non-significant alterations in average body weight. Results suggest that HBEE was more effective than HBAE and gemfibrozil in reducing body weight.

Effects of HBAE and HBEE on Plasma Lipid Profiles

The results of the plasma lipid profile are presented in Table 3. When compared to the normal control, the hyperlipidaemic control group, showed significant ($p < 0.05$) induction hyperlipidemia, which was indicated by elevation of plasma lipids including TC, TG, LDL, and VLDL and reduction of plasma HDL level. When compared to the hyperlipidaemic control group, the gemfibrozil, HBAE, and HBEE treated group showed significant ($p < 0.05$) restoration in plasma lipid profile. The results indicate that HBEE has better hypolipidemic effects than HBAE and gemfibrozil.

Effects of HBAE and HBEE on Plasma Glucose Level

The result is presented in Fig. 2. The hyperlipidemic control rats showed significantly ($p < 0.05$) high plasma glucose levels than the normal control. Moreover, oral administrations of HBAE and HBEE significantly ($p < 0.05$) decreased plasma glucose levels as compared to hyperlipidemic control (Fig. 2). The results indicate that HBEE showed a better anti-hyperglycemic effect than HBAE.

Discussion

The present study was designed to investigate the hypolipidemic effects of HBAE and HBEE and their effect on plasma glucose and body weight gain in a high-fat-diet-induced hyperlipidaemic animal model. Increasing consumption of carbohydrates, fat and excess energy in the diet is a leading cause of obesity.[20] Obesity causes the elevation of lipids concentration in the blood and it may lead to hyperlipidemia.[21] When compared to the normal group, male wistar albino rats of the hyperlipidaemic control group were kept on a high-fat diet, and average body weight and plasma TC, TG, and LDL levels were increased significantly. Whether TC or TG levels increased, or both increased, they are referred to as hyperlipidemia. It suggests that high-fat diet composition was sufficient to produce hyperlipidemia within 4 weeks. Hyperlipidemia,

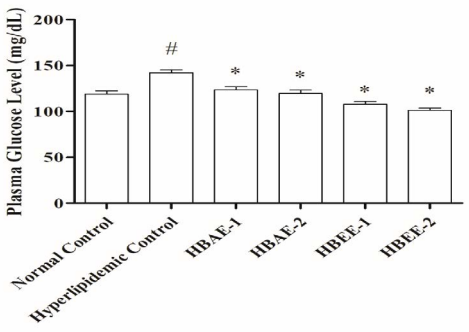

Fig. 2: Effects of HBAE and HBEE on Plasma Glucose Level. Values are expressed as mean ± S.E.M., (n= 6). $^{\#}P < 0.05$ significant values as compared to the normal control group. $^{*}P < 0.05$ significant values as compared to hyperlipidaemic control (one-way ANOVA followed by Turkey posthoc test)

Table 3: Plasma Lipids Level after oral administration of HBAE and HBEE

	TC (mg/dL)	*TG (mg/dL)*	*LDL (mg/dL)*	*VLDL (mg/dL)*	*HDL (mg/dL)*
Normal Control	78.94 ± 2.85	83.31 ± 2.16	24.36 ± 1.80	17.46 ± 0.43	37.11 ± 0.89
Hyperlipidaemic Control	129.11 ± 2.46$^{\#}$	172.35 ± 3.33$^{\#}$	62.46 ± 3.37$^{\#}$	34.47 ± 0.67$^{\#}$	32.17 ± 0.92$^{\#}$
Standard	99.82 ± 3.0*	105.15 ± 2.71*	36.57 ± 4.30*	21.03 ± 0.54*	42.22 ± 1.16*
HBAE-1	113.57 ± 3.75*	124.52 ± 1.74*	47.42 ± 3.78*	24.90 ± 0.35*	41.24 ± 0.42*
HBAE-2	103.08 ± 2.40*	113.51 ± 1.74*	37.84 ± 1.88*	22.70 ± 0.35*	42.54 ± 0.58*
HBEE-1	99.32 ± 2.71*	99.68 ± 2.10*	36.26 ± 2.82*	19.94 ± 0.42*	43.12 ± 0.85*
HBEE-2	90.22 ± 2.33*	91.23 ± 1.40*	25.28 ± 2.24*	18.25 ± 0.28*	46.69 ± 0.73*

Values are expressed as mean ± S.E.M., (n= 6). $^{\#}P < 0.05$ significant values as compared to the normal control group. $^{*}P < 0.05$ significant values as compared to hyperlipidaemic control (one-way ANOVA followed by Turkey posthoc test)

hyperglycemia, and obesity may occur due to cholesterol, bile acid, sucrose, and high fat present in high fat diets. Cholesterol and bile acid induce hypercholesterolemia by interfering with cholesterol absorption, metabolism, degradation, serum clearance, and excretion.[22, 23] Sucrose induces insulin resistance and hypertriglyceridemia[24, 25] and obesity due to higher contents of fats[26]

Results of the present study show that, when compared to the hyperlipidemic control group, the HBAE and HBEE treatments in their respective group, significantly reduced average body weight, plasma lipids such as TC, TG, LDL, and VLDL, and significantly increased the cardioprotective HDL level. The observations indicate that the HBEE at 200 mg/kg had potent hypolipidemic effects, the effects were more pronounced and better than the HBAE.

It is well known that elevated TC and LDL levels are major coronary risk factors.[27] However, reduced HDL is an independent risk factor for atherosclerosis. Additionally, a study on HDL intervention found that a 1% rise in HDL was linked to a 3% decrease in the developing clinical atherosclerosis and coronary risk.[28] Considering the enhancement of cardioprotective lipid HDL after administration of HBAE and HBEE, it can be concluded that the leaves of *H. benghalensis* have potent cardioprotective action and this effect may be due to the increase in activity of lecithin cholesterol acyltransferase (LCAT) which contribute to the regulation of blood lipids.[29] LCAT is essential for converting free cholesterol to HDL and transporting it back to VLDL or IDL, which the liver cells then absorb.[30, 31] The decreased serum TG level is also an important finding of this experiment because TG is also independently related to cardiovascular and this effect might be related to an increase in the endothelium-bound lipoprotein lipase which hydrolyses the triglycerides into fatty acids.[32]

Increased TC/HDL and LDL/HDL ratios (Table 4) are also predictors of coronary risk.[27, 33] A ratio of TC/HDL is more than 4.5 is associated with increased coronary heart disease (CHD) and its ideal ratio is ≤ 3.5.[34, 35] In the present study, these ratios were markedly restored by HBAE and HBEE (Table 4). It may lead to the removal of cholesterol from peripheral tissue to the liver for catabolism and excretion.[36]

Table 4: The ratio of the plasma lipid fraction

	TC/HDL	*LDL/HDL*
Normal control	2.12 ± 0.04	0.65 ± 0.04
Hyperlipidemic control	4.04 ± 0.18$^{\#}$	1.96 ± 0.15$^{\#}$
Standard	2.38 ± 0.12*	0.88 ± 0.12*
HBAE-1	2.75 ± 0.08*	1.15 ± 0.09*
HBAE-2	2.42 ± 0.04*	0.89 ± 0.04*
HBEE-1	2.30 ± 0.06*	0.84 ± 0.07*
HBEE-2	1.93 ± 0.05*	0.54 ± 0.05*

Values are expressed as mean ± S.E.M., (n= 6). $^{\#}P < 0.05$ significant values as compared to the normal control group. $^{*}P < 0.05$ significant values as compared to hyperlipidaemic control (one-way ANOVA followed by Turkey posthoc test)

In addition, metabolic disorders induced by a high-fat diet are associated with hyperglycemia[37] which is reflected in our study. The chronic treatment of HBAE and HBEE led to a significant reduction in blood glucose levels as compared to the hypolipidemic control group. The results indicate that HBEE had better anti-hyperglycemic effects as compared to HBAE.

The phytochemical screening revealed the presence of phytoconstituents such as carbohydrates, alkaloids, flavonoids, saponins, tannins, phenolic compounds, and steroids in HBEE, while HBAE contains flavonoids, saponins, tannins, and phenolic compounds only. These phytoconstituents might be responsible for the hypolipidemic of HBAE and HBEE.

Saponins were reported to reduce blood cholesterol by competing with cholesterol-binding sites or interfering with cholesterol biosynthesis.[35,38] Moreover, saponins form insoluble complexes with cholesterol in the intestine, interfering with absorption.[39] Polyphenols and tannins have been shown to have anti-obesity, hypolipidemic, and hypoglycemic effects in obese and diabetic rats by suppressing dyslipidemia, hepatosteatosis, and oxidative stress,[26, 40] thus, it might be responsible for lowering TC and LDL and elevating HDL in hyperlipidemic rats. Flavonoids have been shown to lower LDL levels and increase LDL oxidation resistance of the body, which

could inhibit atherosclerosis.[11,41] Flavonoids also inhibit lipogenesis by stimulating lipoprotein lipase and plasma LCAT and enhancing cholesterol degradation.[10]

The presence of β-sitosterol in *H. benghalensis* is already reported.[42] β -sitosterol is a plant sterol that is reported as a cholesterol-lowering agent.[30, 43] Literature concern that β-sitosterol reduced the absorption of cholesterol by 42% in a meal containing 500 mg of cholesterol.[44] Therefore, β-sitosterol might be one of the bioactive phytoconstituent in the leaves of *H. benghalensis* which is responsible for a decrease in the plasma cholesterol by reducing cholesterol absorption.

Conclusion

The present study recapitulates the effects of high-fat diet content on a generation of hyperlipidemia and hyperglycemia. The overall results suggest that *H. benghalensis* has potent hypolipidemic effects as well as reducing body weight gain and blood glucose levels. It may improve lipid metabolism and reverse the hyperlipidaemic effects. Phytochemical analysis revealed the presence of various phytoactive constituents. Thus, needs to isolation for further pharmacological evaluations and identification of their mode of action.

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