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EVALUATION OF ANTIOBESITY ACTIVITY OF *TINOSPORA CORDIFOLIA* STEMS IN RATS

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ABSTRACT

The present study was undertaken to investigate the effect of petroleum ether extract of *Tinospora cordifolia* stems (Family: Menispermaceae) on obesity in rats using cafeteria diet- and antipsychotic drug (sulpiride)-induced obesity. Cafeteria diet administered for 40 successive days to Wistar male rats significantly increased body weight, serum total cholesterol, triglycerides and glucose levels; and decreased HDL cholesterol as compared to control. Antipsychotic drug (sulpiride) administered to Wistar female rats for 28 successive days significantly increased the levels of glucose, triglycerides, cholesterol and there was no significant effect on HDL-cholesterol as compared to control. Petroleum ether (50 and 100 mg/kg, p.o.) extract of *Tinospora cordifolia* administered for 40 and 28 successive days showed significant antiobesity effect in cafeteria diet- as well as sulpiride-induced obese rats respectively, as indicated by significant decrease in body weight and serum cholesterol, glucose and triglycerides; and significant increase in HDL-cholesterol as compared to respective cafeteria diet and sulpiride treated control rats. The antiobesity effect of petroleum ether extract of *T. cordifolia* might be due to increase in dopaminergic transmission, since the extract protected the animals against sulpiride-induced obesity. Thus, petroleum ether extract of *Tinospora cordifolia* may be explored further for its potential in treatment of obesity.

KEYWORDS: Obesity, *Tinospora cordifolia*, cafeteria diet, sulpiride

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INTRODUCTION

Obesity is defined as an increase in total fat mass and it occurs when unilocular adipocytes show hyperplasia or hypertrophy following macrophage infiltration of fat tissue[1]. Although a number of pharmacological approaches for treatment of obesity have been investigated, but only few are safe and all of these have adverse effects[2]. So alternative is to discover antiobesity drugs from plants. So aim of the present study was to evaluate antiobesity activity of *Tinospora cordifolia*.

Tinospora cordifolia (Willd.) Miers (Family: Menispermaceae) is a well known plant of Indian medicinal system. Stems of the plant have been reported to possess memory enhancing[3], antistress[4], antidepressant[5], anti-inflammatory[6], antiischemic[7], antioxidant[8], antifertility[9], antiallergic[10] and antineoplastic[11] activities. Ethyl acetate, dichloromethane, chloroform, hexane, methanol, ethanol and aqueous extracts of *Tinospora cordifolia* stems showed hypoglycemic activity[12-14] and its aqueous extract reversed hyperglycemia, hyperinsulinemia, hypertriglyceridemia, insulin resistance, and elevated levels of hepatic total lipids, cholesterol, triglycerides and free fatty acids in fructose-fed rats[15]. But there are no reports on weight reducing and hypolipidemic activities of petroleum ether extract of *Tinospora cordifolia* stems, so we evaluated antiobesity activity of this extract in cafeteria diet- and sulpiride-induced obese rats.

MATERIALS AND METHODS

Experimental animals

Wistar albino rats of either sex, 4-5 weeks old and weighing around 30-40 g were purchased from Disease Free Small Animal House, Chaudhary Charan Singh Haryana Agricultural University, Hisar (Haryana). Male and female animals were housed separately in groups of 5-6 per cage (Polycarbonate cage

size: 45×30×17 cm) under laboratory conditions with alternating light and dark cycle of 12 h each. The animals had free access to food and water. The animals were kept fasted 2 h before and 2 h after drug administration. The animals were acclimatized for at least five days before the commencement of experiments. The experimental protocol was approved by Institutional Animals Ethics Committee (IAEC) and animal care was taken as per the guidelines of Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA), Govt. of India (Registration No. 0436).

Drugs and chemicals

Sulpiride (Sigma-Aldrich, St. Louis, USA), Tween 80 (Loba Chemie, Mumbai). Ethanol(95%), Petroleum ether (40-60^{o}C) AR (Sd Fine-Chem Ltd., Mumbai), diethyl ether LR and glacial acetic acid (Sd Fine-Chem Ltd., Mumbai), kits for estimation of serum glucose, cholesterol, HDL, triglycerides (Crest Biosystems, Division of Coral Clinical Systems, Goa) were used in the present study.

Collection of plant material

The stems of *Tinospora cordifolia* were collected from Kaithal (Haryana), dried under shade followed by oven drying and then, got identified as *Tinospora cordifolia* (Willd.) Miers ex Hook f. & Thomas from Raw Materials, Herbarium and Museum Division, National Institute of Science Communication and Information Resources, New Delhi (Reference number NISCAIR/RHMD/Consult/2010-11/1479/77.

Preparation of extract of *Tinospora cordifolia*

The dried stems were grounded to coarse powder. About 500gm of powdered stems were extracted in petroleum ether (40-60°C) using Soxhlet apparatus at 50^{o}C till siphoning solution became colorless. Now, solvent was recovered by distillation and the extract was dried by using water bath at 40°C. The dried extract was brownish-green in color and the yield was 0.92%w/w. The dried extract was stored in air tight container and kept in a refrigerator[5].

Vehicles

The petroleum ether extract of *T. cordifolia* was emulsified in 10% v/v Tween 80 followed by addition of distilled water to the required strength. Sulpiride was dissolved in normal saline followed by the addition of one drop of glacial acetic acid.

Laboratory models employed for induction of obesity

Cafeteria diet -induced obesity

The composition of Cafetria diet was same as followed earlier[16], but with slight modification. In the present study, bread (25 g) + boiled potato (25 g); condensed milk (25 g) + biscuits (25 g); potato chips (25 g) + rice polish (25 g) were administered to a group of male rats for one week in rotation for a total period of 6 weeks. These diets were given in addition to normal diet.

Antipsychotic drug (sulpiride)-induced obesity

Sulpiride (20mg/kg/day, i.p.) was given for 28 days to female rats. It induces weight gain, hyperphagia, hyperprolactinemia, hypogonadism, and perhaps increased insulin sensitivity in rats[17].

Parameters used to evaluate Obesity

Body weight

Body weights of the animals were measured every week for 6 weeks (for cafeteria-induced obesity) and 4 weeks (for sulpiride-induced obesity).

Biochemical parameters

On day 41 (for cafeteria diet-induced obese rats) and 29th day (for sulpiride diet-induced obese rats), blood samples were withdrawn from retroorbital sinus of animals by glass capillaries. Blood was kept for 30 min for coagulation and then serum was separated by centrifugation at 3000 rpm. Changes in total cholesterol, HDL cholesterol, triglycerides and glucose were measured in serum samples using biochemical kits (Crest Biosystems, Division of Coral Clinical Systems, Goa, India).

Experimental protocols

Animals were divided into 8 groups and each group comprised of a minimum of 5 rats.

Evaluation of antiobesity activity by employing cafeteria diet-induced obesity model in male rats.

Group 1 (n = 5): Vehicle treated control group: 10% v/v Tween 80 in distilled water was administered orally for 40 consecutive days.

Group 2 (n = 5): Cafeteria diet treated control: cafeteria diet was administered for 40 consecutive days.

Group 3 and 4 (n = 5 each): Petroleum ether extracts of *Tinospora cordifolia* (50 and 100 mg/kg p.o. respectively) was administered followed by administration of cafeteria diet after a gap of 2 h for 40 consecutive days. The doses of the extract were selected on the basis of earlier study from our laboratory (Dhingra and Goyal, 2008).

Evaluation of antiobesity activity by employing antipsychotic drug (Sulpiride)-induced obesity model in female rats

Group 5 (n = 6): Vehicle treated control group: 10% v/v Tween 80 in distilled water was administered orally for 28 consecutive days.

Group 6 (n = 6): Sulpiride treated control: Sulpiride (20 mg/kg i.p.) was administered for 28 consecutive days.

Group 7 and 8 (n = 6 each): These were same as groups 3 and 4 for cafeteria diet -induced obesity, except

sulpiride was administered 2 h after administration of the extract for 28 consecutive days

Statistical analysis

All values were expressed as mean ± SEM. The data obtained from various groups were statistically analyzed using one way ANOVA followed by Dunnett's t-test. The p value <0.05 was considered to be statistically significant

RESULTS

Effect of *Tinospora cordifolia* on body weight in cafeteria diet-induced obese rats

Cafeteria diet significantly increased the body weight as compared to vehicle treated control after 1 week of treatment and continued up to 6 weeks. Petroleum ether extracts (50mg and 100mg/kg p.o.) significantly decreased the body weight in cafeteria diet-induced obese rats after 5 and 6 weeks of treatment (Table 1).

Effect of *Tinospora cordifolia* on various biochemical parameters in cafeteria diet-induced obese rats

Cafeteria diet significantly increased the levels of glucose, triglycerides, cholesterol and significantly decreased HDL-cholesterol levels as compared to vehicle treated control. Petroleum ether extracts (50mg and 100mg/kg p.o.) administered along with cafeteria diet for 40 successive days to rats significantly decreased the cholesterol, glucose, triglycerides and increased HDL-cholesterol levels as compared to cafeteria diet-induced obese rats (Table-2).

Effect of *Tinospora cordifolia* on body weight in sulpiride-induced obese rats

Sulpiride significantly increased the body weight as compared to vehicle treated control rats after 1 week of treatment and continued up to 4 weeks. Petroleum ether extracts (50mg and 100mg/kg p.o.) significantly decreased the body weight in sulpiride-induced obese rats after 3 and 4 weeks of treatment (Table 3).

Effect of *Tinospora cordifolia* on various biochemical parameters in sulpiride-induced obese rats

Sulpiride significantly increased the levels of glucose, triglycerides, cholesterol and there was no significant effect on HDL-cholesterol as compared to control. Petroleum ether extract (50mg and 100mg/kg p.o.) administered for 28 successive days to rats significantly decreased the glucose, triglycerides and increased the HDL-cholesterol levels as compared to sulpiride-induced obese rats (Table 4).

DISCUSSION

In the present study, petroleum ether (50 and 100 mg/kg, p.o.) extract of *Tinospora cordifolia* stems produced significant decrease in body weight, serum cholesterol, glucose and triglycerides; and significant increase in HDL-cholesterol in cafeteria diet- and sulpiride-induced obese rats. This is the first study showing hypolipidemic and weight reducing activities of petroleum ether extract of *T. cordifolia* stems.

Cafeteria diet-induced obesity model is the simplest obesity-induction model and possibly the one that most closely resembles the reality of obesity in humans[18]. The results of the present study showed that rats fed with a variety of highly palatable, energy rich, high carbohydrate cafeteria foods elicited significant increase in body weights and serum cholesterol, triglycerides, glucose; and decrease in serum HDL-cholesterol. Cafeteria diets have been previously reported to increase energy intake and cause obesity in humans[19] as well as animals[20]. Further the composition[21,22] and variety[23,24] of cafeteria foods also exert synergistic effects on the development of obesity. The cafeteria diet has been reported to induce hyperphagia in rats[25] which results in higher fat stores[26]. Moreover, the down regulation of striatal D_2 receptor expression is a notable neuroadaptive response to over consumption of palatable food. Indeed, reductions in striatal D_2 receptor density are seen in overweight individuals[27,28] .

Excessive body weight gain and hyperphagia is frequently observed during chronic administration (3-4 weeks) of antipsychotic drugs, such as sulpiride in female rats[16]. In the present study, sulpiride administered for 4 weeks significantly increased body weights of rats and also significantly increased serum cholesterol, triglycerides and glucose levels. Sulpiride induces obesity by two mechanisms- (i) Direct stimulation of feeding related areas in the brain[16,29,30] (ii) Metabolic and endocrine abnormalities secondary to hyperprolactinemia[31,32]. Furhter, sulpiride is devoid of sedative and motor defects; and induces hyperprolactinemia which may cause impairment in reproductive hormones that may promote weight gain[33].

In this study, antiobesity-like effect of petroleum ether extract of *T. cordifolia* might be due to- (i) weight reducing effect of the extract (ii) increasing dopaminergic transmission, since the extract protected the animals against sulpiride-induced as well as cafeteria diet-induced obesity (iii) enhanced thermogenesis since obesity is associated with defective thermogenesis[34]. Phytochemical screening indicated the presence of alkaloids, glycosides, carbohydrates, sterols, polyphenolic compounds, tannins and flavonoids in petroleum ether extract of *Tinospora cordifolia*[5]. Antiobesity activity of petroleum ether extract might be due to the presence of tannins and flavonoids. It has been reported that tannins[35] and flavonoids[36] may be responsible for prevention of obesity. However further study is required to find out the particular component(s)

present in the petroleum ether extract responsible for its antiobesity activity. Thus, petroleum ether extract of *Tinospora cordifolia* may be explored further for its potential in treatment of obesity.

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Table 1: Effect of *Tinospora cordifolia* on body weight of rats in cafeteria diet-induced obesity model

Group no.	Treatment for 40 days p.o.	Dose (kg^{-1})	Body Weight (g)						
			week 0	week 1	week 2	week 3	week 4	week 5	week 6
1	Vehicle treated control	10 ml	34.2±0.7	36±0.7	37.8±0.9	42.2±1.9	46.2±1.9	52.6±1.4	52.2±1.0
2	Cafeteria diet	ad libit-um	34.4±0.7	63.4 ±2.0 [a]	78.6 ±3.5[a]	95.2 ±3.7[a]	103.2 ± 4.0[a]	114 ±5.0 [a]	113.6 ±3.9[a]
3	Pet ether extract + Cafeteria diet	50mg	34.8±1.6	62.2±2.9	80.4±5.4	91.8±2.1	89.4±2.8	82.2 ± 4.5[b]	79.6 ±4.8[b]
4	Pet ether extract + Cafeteria diet	100mg	34.4±0.9	65±3.4	69.4±3.8	93 ± 4.0	93.6±4.5	88± 4.5 [b]	85.4 ±4.6 [b]

n = 5 in each group; Values are in Mean ± SEM; Data was analyzed by one-way ANOVA followed by Dunnett's t-test.
'a' indicates comparison to vehicle treated control at similar weekly intervals.
'b' indicates comparison to cafeteria diet treated animals at similar weekly intervals.

F (3, 16) = 31.29; p < 0.001 (Week 1)
F (3, 16) = 37.40; p < 0.001 (Week 2)
F (3, 16) = 70.46; p < 0.001 (Week 3)
F (3, 16) = 53.66; p < 0.001 (Week 4)
F (3, 16) = 36.92; p < 0.001 (Week 5)
F (3, 16) = 42.11; p < 0.001 (Week 6)

Table 2: Effect of *Tinospora cordifolia* on cholesterol, triglycerides, glucose and HDL levels of rats in cafeteria diet-induced obesity model

Group no.	Treatment for 40 days p.o.	Dose (kg^{-1})	Cholesterol	Triglycerides	Glucose	HDL-Cholesterol
1	Vehicle treated control	10 ml	44.76±2.09	73.53±2.59	88.14±2.78	35.41±1.26
2	Cafeteria diet	ad libitum	136.4±1.99 [a]	169±2.32[a]	133.38±1.75[a]	18.44±0.78 [a]
3	Pet ether extract + Cafeteria diet	50mg	54.92±2.00[b]	84.11±1.69 [b]	90.82±2.67 [b]	33.4±0.94 [b]
4	Pet ether extract + Cafeteria diet	100mg	100.42±2.29 [b]	122.74±3.3 [b]	105.16±2.15 [b]	24.08±0.70

n = 5 in each group; Values are in Mean (mg/dl) ± SEM; Data was analyzed by one-way ANOVA followed by Dunnett's t-test.

F (3, 16) = 409.52; p < 0.001 (Cholesterol)
F (3, 16) = 292.62; p < 0.001 (Triglycerides)
F (3, 16) = 73.363; p < 0.001 (Glucose)
F (3, 16) = 71.521; p < 0.001 (HDL- Cholesterol)
'a' indicates comparison to vehicle treated control at similar weekly intervals.
'b' indicates comparison to cafeteria diet treated animals at similar weekly intervals.

Table 3: Effect of *Tinospora cordifolia* on body weight of rats in sulpiride-induced obesity model

Group no.	Treatment for 28 days p.o.	Dose (kg^{-1})	Body Weight (g)				
			week 0	week 1	week 2	week 3	week 4
1	Vehicle treated control	10 ml	36.2±0.8	36.73±0.9	41.2±1.5	44.66±1.6	50.46±1.24
2	Sulpiride	20 mg	36.56±0.46	47.2±1.75 [a]	57.6 ± 1.88 [a]	61.7 ±2.13 [a]	69.9 ±2.9 [a]
3	Pet ether extract + Sulpiride	50mg + 20 mg	34.06±1.41	40.8±2.0	54.43 ± 1.24	52.53 ± 1.81 [b]	48.61±1.69 [b]
4	Pet ether extract + Sulpiride	100mg + 20 mg	32.66±2.06	47.5±2.89	58.48 ± 1.56	52.41 ± 1.45 [b]	49.5 ±1.98 [b]

n = 6 in each group; Values are in Mean ± SEM; Data was analyzed by one-way ANOVA followed by Dunnett's t-test.
'a' indicates comparison to vehicle treated control at similar weekly intervals.
'b' indicates comparison to sulpiride treated animals at similar weekly intervals.

$F(3, 20) = 6.77$; $p < 0.001$ (Week 1)
$F(3, 20) = 26.25$; $p < 0.001$ (Week 2)
$F(3, 20) = 15.56$; $p < 0.001$ (Week 3)
$F(3, 20) = 24.93$; $p < 0.001$ (Week 4)

Table 4: Effect of *Tinospora cordifolia* on cholesterol, triglycerides, HDL and glucose levels of rats in sulpiride-induced obesity model

Group no.	Treatment for 28 days p.o	Dose (kg^{-1})	Cholesterol	Triglycerides	Glucose	HDL-Cholesterol
1	Vehicle treated control	10ml	45.06±1.73	72.59±2.31	85.43±2.27	35.34±1.02
2	Sulpiride	20mg	69.45±1.60[a]	101.69±1.72 [a]	127.39±1.65 [a]	31.21±1.47
3	Pet ether extract + Sulpiride	50mg + 20 mg	36.75±1.07[b]	89.75±1.02 [b]	94.93±0.60 [b]	43.61±0.83 [b]
4	Pet ether extract + Sulpiride	100mg + 20 mg	43.56±0.90 [b]	90.92±2.03 [b]	108.10±1.64 [b]	37.51±1.03 [b]

n = 6 in each group; Values are in Mean (mg/dl) ± SEM. Data was analyzed by one-way ANOVA followed by Dunnett's t-test.
'a' indicates comparison to vehicle treated control at similar weekly intervals.
'b' indicates comparison to sulpiride treated animals at similar weekly intervals.

$F(3, 20) = 108.84$; $p < 0.001$ (Cholesterol)
$F(3, 20) = 42.82$; $p < 0.001$ (Triglycerides)
$F(3, 20) = 120.81$; $p < 0.001$ (Glucose)
$F(3, 20) = 21.48$; $p < 0.001$ (HDL- Cholesterol)

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