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ANTI-OBESITY ACTIVITY OF METHANOLIC EXTRACT OF *TRICHOLEPIS GLABERRIMA*

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Abstract:

Obesity is very serious and concerned problem these days. Despite availability of many drugs in market to treat obesity, no single drug is ideal for treating all sorts of problems caused by obesity. The obesity models available for inducing obesity are by using chemicals and high fat diet. Wistar albino rats were used to study anti-obesity activity of methanolic extract of Tricholepisglaberrima plant aerial parts at doses 100 mg/kg p.o. and 200 mg/kg p.o. against the standard orlistat 50 mg/kg p.o. in models of anti-obesity activity viz. High fat induced obesity, Monosodium glutamate induced obesity model. The induction of obesity is done by diet (20 grams/animal/day) and Monosodium glutamate (oral). The study period is 28 days for both models. In both models, the plant showed anti-obesity activity significantly at a dose of 100mg/kg and 200 mg/kgp.o. by reducing the body weight, fat pads weight, total cholesterol, triglycerides, LDL, VLDL, biomarkers enzymes like SGOT, SGPT and ALP, whereas significant increase in HDL levels was observed. Further multiple dose pre-clinical studies and clinical studies have to be carried out for proving for human obesity treatment.

Key words: *Tricholepisglaberrima, anti-obesity, Cholesterol, HFD, MSG*

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INTRODUCTION:

Obesity is a common health disorder of lipid and carbohydrate metabolism resulting from excessive fat accumulation in adipose tissue, liver, skeletal muscle etc. (WHO 2011) Obesity, defined as a body mass index (BMI) of more than or equals to 30 kg/m^2, has reached epidemic proportions worldwide, with an estimated 97 million adults in the USA overweight or obese [1]. Obesity substantially raises the risk of morbidity from dyslipidemia [2], fatty liver [3], type 2 diabetes mellitus (T2DM) [4], coronary heart disease and stroke, hypertension [5], gallbladder disease, osteoarthritis, sleep apnea and respiratory problems, endometrial, breast, prostate and colon cancers [6].

In the recent years, there has been a great increase in the use of herbal drugs for the treatment of obesity [7]. Animal models are useful tools for obesity research as they readily gain weight when fed with high fat diet (HFD) and Mono Sodium Glutamate (MSG). The rats fed with HFD and MSG develops obesity, hyperglycemia and hypertriglyceridemia. The physiological aspects of this model replicate many of the human obesity syndrome. Therefore, the HFD and MSG fed models have a good potential to extrapolate animal data for the clinical studies.

The present study was undertaken to evaluate the Antiobesity activity on hyperlipedemia of methanolic extract of *Tricholepisglaberrima*in HFD and MSG induced obesity in rats.

Plant literature

Tricholepisglaberrima(Asteraceae), commonly known as "Brahmadandi" is an important medicinal plant used in our traditional system of medicine to treat various diseases.

The plant contains flavonoids, triterpenoids, saponin glycosides and sterols betulin, spinasterol, stigmasterol, stigma 7 enol and ariterpenoid-cycloart-23-en-3 beta, 25 diol [8].

Methanol, chloroform, aqueous extract of aerial parts of *Tricholepisglaberrima*had prooved Aphrodisiac activity [9],antioxidant activity [10], ameliorative effects in hepatic damage[11], neuropharmacological activity [12].

Experimental Methods:

Acute Toxicity Study

The acute toxicity studies of *Tricholepisglaberrima* were carried out as per OECD guidelines 423. There was no gross evidence of any abnormalities observed up to a period of 4-6hrs and no mortality was observed at the maximum tolerated dose (MTD) level of 2000mg/kg p.o. The maximum tested dose was 2000mg/kg body weight. Further pharmacological screenings were carried out with two dose ranges i.e. 1/20 of MTD (100mg/kg p.o.), 1/10 of MTD (200mg/kg p.o.). They were taken as Test doses T_1 and T_2 respectively.

MATERIALS AND METHODS:

Collection and authentification

The areal parts of the plant were collected from Tirupathi, authenticated by Botanist Dr K. Madhavshetty at Sri Venkateshwara University.

Animals

72 Healthy adult, Albino Wistar rats of either sex, 8-10 weeks old, weighing about 150-200 gms were used in the experiment. Animals were housed in polypropylene cages maintained under standard conditions and provided with standard diet and water. All the animals were acclimatized to the laboratory conditions for a week before the commencement of the experiment. The experimental protocol was approved by the Institutional Animals Ethics Committee (1821/PO/Re/S/15/CPCSEA) constituted as per CPCSEA guidelines

Extraction of the plant

Fresh aerial parts of the plant *Tricholepisglaberrima*were taken, dried under shade and then coarsely powdered with a mechanical grinder. Dried powder was filtered with sieve of mesh no.20. 300gms of the filtered powder was used for preparing the extract. Methanolic extract of *Tricholepisglaberrima*was prepared by Soxhletion in Soxhlet apparatus for 12hrs. Further the extract was concentrated by evaporating in water bath at 40°c.The yield of extract was 30.27gm and the percentage yield was 15.13%. It was stored in air tight container in refrigerator. The concentrated extract was weighed and dissolved in normal saline to get the desired concentrations for the experiment.

Fat Diet Model (HFD):

Requirements

36 male albino rats weighing between 180-300gms (divided in 6 groups containing 6 each), normal diet, Methanolic extract of *Tricholepisglaberrima* (METG),high fat died (HFD), normal saline. Study duration is 28 days.

Table 1: High Fat Diet Model

Groups	Treatment	Dose
Group I	Normal control group, Normal diet	Normal pellet diet+ normal saline p.o.
Group II	Negative control group HFD	HFD and normal saline p.o.
Group III	Positive control group	Orlistat50 mg/kg
Group IV	Test group (T_1)	100mg/kg METG
Group V	Test group (T_2)	200mg/kg METG
Group VI	Test group (T_3)	400mg/kg METG

Table 3: MSG Model

Groups	Treatment	Dose
Group I	Normal control group, Normal diet	Normal pellet diet + normal saline p.o.
Group II	Negative control group MSG	MSG and normal saline p.o.
GroupIII	Positive control group	Orlistat50 mg/kg in normal saline p.o.
Group IV	Test group (T_1)	100mg/kg METG
Group V	Test group (T_2)	200mg/kg METG
Group VI	Test group (T_3)	400mg/kg METG

Monosodium glutamate model:
Requirements: 30, male albino rats weighing between 180-300gms (divided in 5 groups containing 6 each),normal diet, Methanolic extract of *Tricholepisglaberrima* (METG),Mono sodium glutamate (MSG), normal saline.Animal grouping and their treatment is presented in the following Table 3:

Biological Parameters:
Body weights:
The body weight was recorded on day 1 and then weekly for 4 weeks in each group.

Net weight loss = Initial weight – Final weight.

Liver weights:
Animals were sacrificed by decapitation after the blood is collected. The livers were excised and rinsed with cold physiological saline and are blotted on filter paper. They were then weighed on electronic balance and examined physically.

Biochemical Estimations:

At the end of experimental period (28 days), overnight fasted animals (12hrs) were given mild ether anesthesia and blood was collected by retro orbital sinus puncture in EDTA coated vials. Serum was estimated for the following:

1.Serum lipid profile:

Total cholesterol was measured by enzymatic CHOD-POD end point colorimetry

Triglyceride was measured by enzymatic end point colorimetry

HDL-C was measured by Phosphotungstate method.

LDL-C was measured by Friedelwald's formula.

2. Liver Function Tests:

a. Serum Glutamate Oxaloacetate Transaminase (SGOT)
b. Serum Glutamate Pyruvate Transaminase (SGPT)
c. Alkaline Phosphatase (ALP)

Statistical Analysis:

Results were expressed as Mean ± SEM. Statistical analysis were performed with Graph pad instat (Version 3.10) and Prism 6 (Version 6.05) software using one way analysis of variance (ANOVA), followed by Dunnet'st-test.

Preliminary Phytochemical Analysis:
Phytochemical screening of Tricholepisglaberrrima was done using Methanol, the extract showed the presence of Alkaloids, carbohydrates, glycosides, saponins, flavonoids and tannins. Results are shown in the following table.

Table 4: Preliminary Phytochemical Analysis

S.No	Test	Inference
1	Alkaloids	Positive
2	Carbohydrates	Positive
3	Steroids	Negative
4	Glycosides	Positive
5	Saponins	Positive
6	Flavanoids	Positive
7	Triterpinopids	Negative
8	Tannins	Positive
9	Proteins and Amino Acids	Negative

Table 5: Effect of METG on body weights of rats (HFD MODEL)

	Differences in body weights (gm) (Mean ± SEM)			
Group	**Week 1**	**Week 2**	**Week 3**	**Week 4**
Group I	33.2 ± 1.92	36.8 ± 0.9	38.2 ± 1.9	41.20 ± 1.0
Group II	33.4 ± 1.89**	77.6 ± 3.5**	102.3 ± 4.0*	112.6 ± 3.9
Group III	33.4 ± 1.86*	68.4 ± 3.8**	92.6 ± 4.5***	84.4 ± 4.6**
Group IV	33.2 ± 4.5***	79.6 ± 3.1*	99.1 ± 4.3*	95.3 ± 4.1*
Group V	33.8 ± 1.6**	77.4 ± 5.4*	97.4 ± 2.8**	89.54 ± 4.8*
Group VI	33.5± 1.2*	68.5 ± 4.4	93.5 ± 1.6***	87.36 ± 3.5**

Values are expressed as Mean ± SEM (n=5), *p<0.05, **p<0.01, ***p<0.001 was considered significant compared to Control

Group I: Normal control, Group II:Negetive control, Group III: Positive control Orlistat 50mg/kg p.o, Group IV: T_1 - METG 100mg/kg p.o, Group V: T_2 - METG 200mg/kg p.o, Group VI T_3 - METG 400mg/kg p.o

Table 6: Effect of METG on body weights of rats (MSG MODEL)

	Differences in body weights(gm)(Mean±SEM)			
Groups	**Week 1**	**Week 2**	**Week 3**	**Week 4**
Group I	31.2 ± 1.67	37.7 ± 1.79	39.9 ± 1.9	40.80 ± 1.21
Group II	33.4 ± 1.63*	67.6 ± 3.5**	82.3 ± 4.0	88.6 ± 3.9*
Group III	32.4 ± 1.59*	59.4 ± 3.8*	73.6 ± 4.5*	71.4 ± 4.6**
Group IV	31.2 ± 4.5***	71.6 ± 3.1*	80.1 ± 4.3*	85.3 ± 4.1*
Group V	30.08 ± 1.6*	68.4 ± 5.4	77.4 ± 2.8*	79.54 ± 4.8
Group VI	30.04 ± 1.3*	66.54 ± 5.2	77.4 ± 2.8**	74.6 ± 3.5*

Values are expressed as Mean ± SEM (n=6) *p<0.05, **p<0.01, ***p<0.001 was considered significant compared to Control.

Table7: Effects of METG on liver weights of rats (HFD MODEL)

Groups (n=5)	**Liver weights (g)HFD model**	**Liver weights (g)MSG model**
Group I	5.92 ± .23	5.64 ± 0.19
Group II	6.79 ± 0.15**	6.42± 0.17**
Group III	6.15 ± 0.23**	6.04 ± 0.19 **
Group IV	6.57 ± 0.17*	6.37 ± 0.15 *
Group V	6.29 ± 0.16**	6.21 ± 0.17 **
Group VI	6.18±0.13**	6.10±0.18**

Values are expressed as Mean ± SEM (n=6) *p<0.05, **p<0.01, ***p<0.001 was considered significant compared to Control.

Table-8: Effect of METG on Total Cholesterol and Triglyceride levels in HFD and MSG rats

Groups	**Total Cholesterol (mg/dl) (HFD)**	**Total Cholesterol (mg/dl) (HFD)**	**Triglycerides (mg/dl) (MSG)**	**Triglycerides (mg/dl) (MSG)**
Group I	82.13 ± 2.98	74.92 ± 3.62	71.05 ± 1.98	68.52 ± 4.21
Group II	138.43 ± 2.13**	138.57 ± 4.78**	141.87 ± 3.12	98.26 ± 3.28
Group III	96.98 ± 2.04***	92.37 ± 4.49 ***	78.91 ± 3.89***	72.98 ± 4.42 ***
Group IV	125.43 ± 3.65*	130.67 ± 4.56 *	109.98 ± 3.16*	83.98 ± 5.68 *
Group V	118.5± 2.91**	118.89± 5.51**	89.63± 3.87**	78.56 ± 6.02 **
Group VI	101.6± 2.06**	98.01±4.21**	82.03 ± 3.01**	72.46± 4.40**

Values are expressed as Mean ± SEM (n=5)*p<0.05, **p<0.01, ***p<0.001 was considered significant compared to Control.

Table-9:Effect of HFD on HDL, LDL AND VLDL levels in rat

Groups (n=5)	HDL (mg/dl)	LDL (mg/dl)	VLDL (mg/dl)
Group I	32.62 ± 2.12	34.54 ± 2.01	15.39 ± 1.07
Group II	23.87 ± 3.39	88.09 ± 3.12	27.59 ± 3.39**
Group III	30.45 ± 3.97**	49.67 ± 3.96**	17.29 ± 1.87**
Group IV	27.42 ± 1.89*	74.98 ± 2.12*	23.24 ± 1.18*
Group V	28.91 ± 2.98**	71.02 ± 4.14**	19.36 ± 2.25**
GroupVI	30.12 ±2.29*	52.54 ±3.56*	17.23 ±1.95*

Values are expressed as Mean ± SEM (n=5) *p<0.05, **p<0.01, ***p<0.001 was considered significant compared to Control.

Table-10:Effect of METG on HDL, LDL AND VLDL levels in rat

Groups (n=5)	HDL (mg/dl)	LDL(mg/dl)	VLDL(mg/dl)
Group I	32.61 ± 2.02	31.87±2.11	18.73±1.07
Group II	25.98 ± 3.39**	82.87±3.12**	29.65±3.38**
Group III	30.45 ± 3.97**	48.37±3.95**	21.29±1.87**
Group IV	40.64 ± 1.89*	77.98 ±2.21*	30.85 ±1.18*
Group V	35.01 ± 2.98**	71.35±4.14**	26.43±2.25**
GroupVI	33.56 ± 3.02*	58.36 ±2.56*	22.36 ±1.88*

Values are expressed as Mean ± SEM (n=5),*p<0.05, **p<0.01 was considered significant compared to Control.

Table-11:Effect of METG on SGOT, SGPT AND ALP levels in rats

Groups (n=5)	SGOT (IU/L)	SGPT (IU/L)	ALP (IU/L)
Group I	17.34 ± 3.67	22.42 ± 3.65	87.49 ± 4.93
Group II	42.28 ± 2.87	52.85 ± 5.98	246.59 ± 2.98
Group III	21.84 ± 2.91**	23.78 ± 5.92**	97.31 ± 5.24***
Group IV	31.59 ± 3.66*	37.39 ± 4.03*	159.93 ± 3.61**
Group V	24.56 ± 3.75**	32.78 ± 5.02**	123.09 ± 4.63**
GroupVI	22.56 ±2.59*	28.36 ±4.88*	102.84 ± 3.65*

Values are expressed as Mean ± SEM (n=5),*p<0.05, **p<0.01, ***p<0.001 was considered significant compared to Control.

Table-12:Effect of METG on SGOT, SGPT AND ALP levels in rats

Groups (n=5)	SGOT (IU/L)	SGPT (IU/L)	ALP (IU/L)
Group I	26.66 ± 2.69	35.83 ± 4.23	92.12 ± 3.45
Group II	49.33 ± 2.59	59.34 ± 4.16	197.49 ± 3.4
Group III	30.98 ± 3.04**	42.34 ± 4.31**	123.78 ± 3.21***
Group IV	39.59 ± 3.32*	57.83 ± 4.42*	149.87 ± 3.09**
Group V	33.47 ± 3.13**	48.87 ± 4.28**	120.87 ± 3.52**
GroupVI	31.56 ± 3.04*	38.56 ± 4.21*	116.36 ± 3.25*

Values are expressed as Mean ± SEM (n=5)*p<0.05, **p<0.01, ***p<0.001 was considered significant compared to Control.

DISCUSSION:

The etiology of obesity is multifactorial and is reaching prevalent proportions and hasevil effects on health associated with a shorter life expectancy [13] even at low levels. The adverse effects of obesity are very harmful that there is a risk of 20% mortality rate with increase in the 20% of the ideal weight [14].

Many efforts have been made to correct the metabolic disparity of the obesity condition, producing a number of reagents including Fibrates (PPARα agonist), Sibutramine [15] but none of them are free from side effects. Orlistat reduces intestinal fat absorption through inhibition of pancreatic lipase is also not free of from side effects [16]. Hyperlipidemia is widely known to be the major risk factor for the development of cardiovascular diseases. Coronary heart diseases, atherosclerosis,stroke, and hyperlipidemia are the main cause of death. The treatment for hyperlipidemia and arteriosclerosis include thereduction of elevated blood serum/plasma levels of lipids. HMG-CoA reductase inhibitors (Statins), Bile acid sequesterant (Resins) andFibric acid derivativesinhibits triglyceride synthesis which is the major target in treating hyperlipidemia.

In the present study, the anti-obesity and anti-hyperlipidemic activity of methanolic extract of aerial parts of *Tricholepisglaberrima* (METG) was studied using dietary animal models of obesity. There was significant increase in the body weight in both High fat diet (HFD) and Mono Sodium Gutamate (MSG) treated animals, which was significantly reduced by the administration of METG and Orlistat.

By the phytochemical investigation it was found that *Tricholepisglaberrima* contains carbohydrates, alkaloids, flavanoids, saponins, tannins. Sterols, flavanoids, saponins, tannins reducescholesterol levelsand have antioxidants activity. The plant was found to be useful in treatment of obesity and hyperlipidemia might be owing to the existence of above mentioned phytoconstituents.

Increased level of plasma lipoprotein results from increased absorption of cholesterol from the intestine or enhanced endogenous synthesis. Decrease in the dietary cholesterol absorption from the intestine by binding with bile acids within the intestine and increasing bile acid secretion or obstruction of biosynthesis of cholesterol are the two possible mechanisms of observed hypolipidemic activity of plant.

Saponin inhibits pancreatic lipasewhich is akey enzyme responsible for hydrolysis of 50-60% of total dietary fats [17]. Fatty acids and 2-monoacylglycerols are the main products formed by the hydrolysis of pancreatic lipase. These products combine with bile salts, dispersed as micelles and carried in this form to the site of absorption. Absorption of lipids takes place in the apical part of the plasma membrane epithelial cells, so inhibition of this enzyme may cause decrease in fat absorption [18].

The investigation revealed that both models causes increase in serum lipid profiles: Total cholesterol, Triglycerides, LDL and VLDL with decrease in HDL and the liver function test also showed Increase in SGOT SGPT and ALP levels. However, there was significant decrease in TG, TC, LDL, VLDL, SGOT, SGPT and ALP with increase in HDL levels. This may be attributed to the action of METG 200mg/kg BW p.o and Orlistat 50mg/kg BW p.o.

These findings suggest that that the plant *Tricholepisglaberrima* possesses strong antiobesityand anti hyperlipidemic effects which indicate great potential of extracts as metabolic regulators of lipogenic and lipolytic pathways. Preferably this study will lead to a harmless and additional effective pharmacological management for hyperlipedemiaand obesity.

CONCLUSION:

The biological activities of methanolic extract of *Tricholepisglaberrima* observed in this study strongly indicated their great potential as anti-obese and obesity associated complications like hyprlipidemia. Oral administration of extracts reduced the level of circulating lipids significantly, resulting in the decrease of body weights in various animal models of obesity bearing close resemblance to human obesity. Extract appear to show such activities by modulating the lipid metabolism through the decreased activity in lipogenesis or by inhibition of pancreatic lipase activity.

The methanolic extract of aerial parts of *Tricholepisglaberrima* at a dose of 200mg/kg b.w. p.o. significantly reduced total cholesterol, triglycerides, LDL, VLDL, biomarkers enzymes like SGOT, SGPT and ALP, whereas significant increase in HDL levels was observed.

Phytoconstituents like saponins, tannins and flavonoids in METG may be responsible for its anti-obesity and anti-hyperlipidemic activities by multiple actions.

Apart from anti-obesity and anti-hyperlipidemic agent, It may also act as hepatoprotective agent due to possessing significant reduction in SGOT, SGPT and ALP levels and significant increase in HDL levels respectively.

Thus it can be said that METG is effective in ameliorating abnormalities in lipid profile and fat accumulation in rats and results provides useful information for the clinical research that this plant can be used as herbal drug in the treatment of obesity and hyperlipidemia. Further studies on this

extract may be focused on the possible mechanism of action, isolation, characterization and purification of active constituents which is responsible for anti-obesity and anti-hyperlipidemic activities.

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