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Original research

Effect of ethanolic extract of *Cuscuta reflexa* on high fat diet- induced obesity in Wistar rats

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ABSTRACT

Objective: The objective of the study was to evaluate the anti-obesity effect of ethanolic extract of *Cuscuta reflexa* on high fat diet induced obesity in Wistar rats.
Methods: In the present study, male Wistar rats were selected and fed with HFD for 4 weeks. They were then treated with different doses of *Cuscuta reflexa* (200 and 100 mg/kg/day, p.o.o.d.) for 6 weeks along with HFD. Orlistat (30 mg/kg/day, p.o.o.d.), a potent lipase inhibitor and standard drug for obesity was used as a standard control in the present study. The effects of these treatments on body weight parameters, feed intake (Kcal), levels of serum glucose, triglycerides (TGs), total cholesterol (TC), high-density lipoproteins (HDL), and low-density lipoprotein (LDL) were analyzed.
Results: Treatment with ethanolic extract of *Cuscuta reflexa* produced significant dose dependent decrease in the body weight, BMI, Lee's index, feed intake (in Kcal) as compared to HFD treated rats. Oral administration of graded doses of *Cuscuta reflexa* extract caused reduction in the levels of serum TC, TG, LDL, VLDL and glucose and the level of HDL was enhanced as compared to HFD fed group.
Conclusion: The results suggest that administration of *Cuscuta reflexa* can inhibit the development of obesity in HFD-induced obesity.

1. Introduction

Obesity is a complex interplay of environmental, genetic, and psychosocial factors associated with significant morbidity and mortality (McIntyre, 1998). An escalating prevalence of obesity is observed in all age groups of the developed countries (Nammi et al., 2004). It is characterized by accumulation of excess fat in the body to an extent which adversely affects the health (Haslam and James, 2005). It is a direct consequence of perpetual imbalance between food intake and energy expenditure with storage of extra calories in the form of fat in the adipose tissues (Kumar et al., 2014a). Several environmental factors like high-calorie food intake and sedentary life style account for weight gain in individuals. Genetic factors also contribute to this imbalance (Bloom et al., 2008a). Surgical intervention may be necessary in extremely obese cases. (see Tables 1 and 2)

Apart from diet and physical exercise anti-obesity drugs have also come into play in management of obesity as they reduce appetite and inhibit absorption of fat (Demelo et al., 2009). Many novel synthetic compounds are being investigated with simultaneous emphasis on exploring natural materials as alternative therapies. Countless herbal interventions are now available for speedy weight loss by enhancement of satiety and boosting metabolism and can be used efficiently as anti-obesity drugs (Gosh, 2009).

Cuscuta reflexa is a potent medicinal plant and is known for its multiple therapeutic activities like antiviral, anticonvulsant, bradycardia, anti-steroidogenic, antispasmodic and hemodynamic agent since a long time (Costa-Lotufo et al., 2005). The detailed study of the plant including its antioxidant, free radical scavenging and 5-alpha reductase inhibitor activity led to the idea of evaluation of its anti-obesity properties (Lalchand et al., 2017).

Many in-vitro studies on stems of the plant have been conducted and antioxidant activity (non-enzymatic hemoglobin glycolsylation) has been evaluated (Kumar et al., 2014b). It was observed that *Cuscuta reflexa* reduces oxidative stress and is effective in obesity. Its phyto-constituent profile is highly rich in flavonoids (Kaempferol, quercetin), coumarin and flavonoid glycosides (Ghani, 2003). Kaempferol and quercetin were reported to significantly improve insulin-stimulated glucose uptake in mature 3T3-L1 adiopocytes by acting on multiple targets which ameliorate hyperglycemia (Fang et al., 2008). Decrease in resistance of insulin may highly reduce the chances of obesity. *Cuscuta*

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Table 1
Effect of various pharmacological interventions on the body weight, BMI, Lee index, feed intake in gram and feed intake in Kcal.

Parameters	Initial body weight (g)	Final body weight (g)	BMI (g/cm2)	Lee index (g/cm)	Feed intake (g)	Feed intake (Kcal)
Normal diet treatment						
Group1:Normal control	208.33 ± 14.7	264.16 ± 8.61	0.79 ± 0.04	352.05 ± 8.56	25.33 ± 3.50	96.26 ± 13.30
High-fat diet treatment						
Group2:HFD control	216.66 ± 20.4[a]	360.5 ± 22.6[a]	1.19 ± 0.04[a]	409.86 ± 11.05[a]	22.95 ± 1.04	122.32 ± 8.42[a]
Group3:HFD + Orlistat	204.17 ± 11.14[b]	239.17 ± 14.63[b]	0.81 ± 0.03[b]	361.22 ± 6.55 [b]	14.15 ± 0.48[b]	75.41 ± 02.56[b]
Group4:HFD + *Cuscuta reflexa* extract (Low)	210.5 ± 8.80[b]	245.83 ± 4.92[b]	0.85 ± 0.05[b]	368.95 ± 12.59[b]	16.00 ± 0.45[b]	85.28 ± 2.38[b]
Group5:HFD + *Cuscuta reflexa* extract (High)	219.17 ± 7.36[b]	241.67 ± 4.08[b]	0.82 ± 0.06[b]	361.63 ± 14.68	14.25 ± 0.55[b]	75.95 ± 2.95[b]

All values are expressed as Mean ± S.D; [a] = $p < 0.05$ vs normal diet control, [b] = $p < 0.05$ vs High fat diet.HFD: High-fat diet, BMI: Body mass index.

Table 2
Effect of various pharmacological interventions on the serum glucose and lipid profile.

Parameters	Serum GLU (mg/dl)	Serum TC (mg/dl)	Serum TG (mg/dl)	Serum HDL (mg/dl)	Serum VLDL (mg/dl)	Serum LDL (mg/dl)
Normal diet treatment						
Group1:Normal control	93.32 ± 3.08	99.62 ± 0.82	68.24 ± 3.67	32.27 ± 1.66	13.64 ± 0.73	53.37 ± 1.90
High-fat diet treatment						
Group2:HFD control	159.87 ± 2.56 [a]	158.42 ± 4.03[a]	149.29 ± 1.85 [a]	21.29 ± 0.60 [a]	29.85 ± 0.37 [a]	107.27 ± 3.66 [a]
Group3:HFD + Orlistat	101.35 ± 1.81 [b]	106.72 ± 2.25[b]	76.44 ± 1.26 [b]	33.89 ± 0.26[b]	15.29 ± 0.25[b]	57.54 ± 1.94 [b]
Group4:HFD + *Cuscuta reflexa* extract (Low)	121.79 ± 1.89[b]	125.59 ± 1.55[b]	109.12 ± 1.87[b]	24.94 ± 0.85[b]	21.82 ± 0.37[b]	78.82 ± 1.36[b]
Group5:HFD + *Cuscuta reflexa* extract (High)	110.06 ± 1.03[b]	113.87 ± 2.20[b]	80.46 ± 2.22[b]	30.06 ± 0.85[b]	16.09 ± 0.44[b]	67.71 ± 2.84[b]

All values are expressed as Mean ± S.D; [a] = $p < 0.05$ vs normal diet control, [b] = $p < 0.05$ vs High fat diet.GKU: Glucose, TC: Total cholesterol, TG: Triglycerides, LDL: Low density lipoprotein, VLDL: Very low density lipoprotein, HDL: High density lipoprotein.

reflexa is also a 5-alpha reductase inhibitor (Patel et al., 2014a). 5-alpha reductase is an intracellular enzyme that converts the androgen testosterone into DHT. By blocking DHT production, it may increases the level of testosterone in body, which further reduces the obesity. Inhibition of 5α-reductase also reduces epididymal weight. DHT helps activate the $GABA_A$ receptor, which functions to tamp down signaling among neurons; because *Cuscuta reflexa* prevents the formation of DHT, it may contribute to a reduction of $GABA_A$ activity. . It has been reported in certain studies that the decreased $GABA_A$ activity prevents obesity. Thus, the reduction in $GABA_A$ activity may contribute in the prevention of obesity. Thus the present study was designed to investigate the anti-obesity potential of aqueous extract of *Cuscuta reflexa* in high fat diet induced obesity in Wistar rats.

2. Materials and methods

2.1. Drugs and chemicals

Casein (Anjan Enterprises, Amritsar, India) and Cholesterol (Thomas Baker, Mumbai, India) used to prepare high fat diet. The standardized plant extract (*Cuscuta reflexa*) was purchased from VHCA herbals karnal, Haryana (India). Orlistat (Macleods Pharmaceuticals Ltd., Mumbai 400059, Batch no. TT901, Mfd Date 01/2015, Exp Date 12/2017). The estimation kits for serum glucose, cholesterol, triglycerides and HDL were obtained from ADI Diagnostic [P] Ltd., Vadodara, India. All other chemicals used in the present study were of analytical quality. All the drug solutions were freshly prepared before use.

2.2. Experimental obesity

Experimental obesity was produced by feeding high fat diet (containing; Powdered Normal chow ($C_6H_7N_3O_2$), 365 g; Lard ($C_{21}H_{42}O_5$), 310 g; Casein ($AlK(SO_4)_2 \cdot 12\ H_2O$), 250 g; Cholesterol ($C_{27}H_{46}O$), 10 g; Vitamin mix and mineral mix, 60 g; dl-Methionine ($C_5H_{11}NO_2S$), 3 g; Yeast powder ($C_{19}H_{14}O_{2)}$, 1 g; NaCl, 1 g were added to make 1 kg of diet (Patel et al., 2014a) and were fed to rats for a period of 10 weeks. Mineral mix was composed of NaCl, 5.57 g; KCl, 32 mg; $MgSO_4$, 2.29 g; $FeSO_4.7H_2O$, 108 g; $CaHPO_4$, 70 mg; $CuSO_4.5H_2O$, 0.1 mg; $MnSO_4.H_2O$, 0.01 mg; $ZnSO_4.H_2O$, 28.7 mg; KI, 0.025 mg; $COCl_2.6H_2O$, 9 mg and MgO, 0.15 mg. The vitamin mix contained Retinol acetate ($C_{22}H_{32}O_{2)}$, 5000 IU; cholecalciferol ($C_{27}H_{44}O$), 400 IU; 7-hydrochloride, dehydrocholesterol, 2-nicotinamide, 45 mg; D-panthenol ($C_9H_{19}NO_4$), 5 mg; pyridoxine ($C_8H_{11}NO_3$) 2 mg; ascorbic acid ($C_6H_8O_6$), 75 mg; folic acid ($C_{19}H_{19}N_7O_6$), 1000 μg and cyanocobalamin ($C_{63}H_{88}CoN_{14}O_{14}P$), 5 μg. The High Fat Diet contained 5.33 kcal/g while the normal chow contains 3.80 kcal/g.

INGREDIENTS	DIET (g/kg)
Powdered NPD ($C_6H_7N_3O_2$)	365
Lard ($C_{21}H_{42}O_5$)	310
Casein ($AlK(SO_4)_2 \cdot 12\ H_2O$)	250
Cholesterol ($C_{27}H_{46}O$)	10
Vitamins and minerals mix	60
Methionine ($C_5H_{11}NO_2S$)	03
Yeast powder ($C_{19}H_{14}O_{2)}$	01
Sodium chloride (NaCl)	01

2.3. Experimental animals and design

Wistar albino rats of either sex, weighing 150–220 g were employed in the study. They were fed on standard chow diet (Ashirwad Industries Pvt Ltd, Ropar, and Punjab, India) or high fat diet (composition given below). Food and water were provided ad libitium throughout experimental period. They were housed in departmental animal house and were exposed to 12 h light and 12 h dark cycles. All animals were maintained as per the CPCSEA guidelines for the care and use of Laboratory Animals, the experimental protocol used in the study was approved by Institutional Animal Ethics Committee. All animals were randomly divided into different five groups (n = 6).

2.3.1. Group I: {normal control}

Normal Rats were maintained on standard chow diet and water *ad libitum* for 10 weeks.

2.3.2. Group II: {high fat diet}

High fat diet was administered to rats for 10 weeks.

2.3.3. Group III: {HFD + Orlistat}

Orlistat (30 mg/kg/day p.o.,*6 weeks) was administered to rats on

high fat diet at the end of fourth week and continued up to the end of the tenth week.

2.3.4. Group IV {100 mg/kg}: {Cuscuta reflexa extract 100 mg/kg/day p.o., 6 weeks}

C.reflexa (100 mg/kg/day p.o., * 6 weeks) was administered to rats on high fat diet at the end of fourth week and continued up to the end of the tenth week.

2.3.5. Group V {200 mg/kg}: {Cuscuta reflexa extract 200 mg/kg/day p.o., 6 weeks}

C.reflexa (200 mg/kg/day p.o., * 6 weeks) was administered to rats on high fat diet at the end of fourth week and continued up to the end of the tenth week.

C.reflexa extract and Orlistat were orally administered to the rats by oral gavages except normal control; all the groups were continually fed the HFD during the experiment. All the animals had free access to water, and the animals were inspected daily. Food intake and body weight were measured twice weekly. At the end of the stipulated period, blood for various biochemical parameters was obtained by retro-orbital puncture under light ether anesthesia, and the animals were sacrificed by cervical dislocation. The blood was collected into tubes, serum separated and analyzed on the same day. The epididymal, mesenteric and retroperitoneal white adipose tissue (WAT) were dissected, cleaned of, weighed and stored in 10% buffered formalin solution. Lee index (Bernardis and Bellimger, 1982), i.e., [body wt. in g]1/3/[ano-nasal length in cm] and body mass index [BMI] (Novellie et al., 2007), i.e., [body wt. in g]/[height in cm2] an index of obesity were calculated at the end of the experiment.

2.4. Estimations

Total cholesterol, High Density Lipoprotein (HDL), Low Density Lipoprotein (LDL), Very Low Density Lipoprotein (VLDL) and Triglycerides, glucose level in serum were also estimated by using commercially available kits.

2.5. Stastical analysis

All values were expressed as mean ± S.D. The data obtained from various groups were statistically analyzed using one way ANOVA followed by Turkey's multiple comparison tests. The p value < 0.05 was considered to be statistically significant.

3. Results

3.1. Effect of various pharmacological interventions on anthropometric parameters

A significant increase ($p < 0.5$) in body weight, BMI and Lee Index was observed in rats fed with high fat diet with increased (in kilocalories) (Kcal) and decreased (in grams) feed intake as compared to rats fed on standard diet. The positive control in the present study which is Orlistat decreases all anthropometric parameters of obesity. However oral supplementation of *Cuscuta reflexa* extract in high and low dose (200 and 100 mg/kg) produced significant ($p < 0.05$) dose dependent reduction in body weight, BMI, Lee index and feed intake (in Kcal) to the HFD fed group as compared to standard diet rats and the results were very near to the positive control group i.e. HFD + Orlistat.

3.2. Effect of various pharmacological interventions on different fat depots

Administration of high fat diet (HFD) for 10 weeks caused a significant ($p < 0.05$) increase in various fat depots like epididymal, retroperitoneal, mesenteric fat depots and increased total fat of the body. Treatment with *Cuscuta reflexa* extract in high and low dose (200 and 100 mg/kg) produced significant ($p < 0.05$) dose dependent decrease in body fat depots: epididymal, retroperitoneal, mesenteric fat and total fat in body as compared to HFD control.

3.3. Effect of various pharmacological interventions on serum biochemical parameters

A significant elevation of serum total cholesterol (TC), triglycerides (TG), LDL, VLDL and decreases in HDL was seen in rats in HFD group as compared to age matched normal rats fed in standard diet. Orlistat, a positive control in present study decreases all the biochemical parameters of obesity. Treatment of high fat diet fed rats with *Cuscuta reflexa* extract in high and low dose (200 and 100 mg/kg) produced a significant ($p < 0.05$) dose dependent reduction in serum total cholesterol (TC), Triglycerides (TG), LDL, VLDL of HFD fed rats and significant increase in the level of HDL as compared to HFD control group and the results closely resembled to the positive control group i.e. HFD + Orlistat.

4. Discussion

In the present study, we disrupted metabolic balance by inducing high fat diet (HFD) in rats and developed experimental obesity. Usually, elevation of plasma lipids (Storlien et al., 1986) characterized with elevated TC, TG levels, LDL-cholesterol levels, and decreased serum HDL-C (Woods et al., 2003) occur when metabolism is disturbed. Moreover, feeding with HFD caused hyperglycemia in rats (Ikemoto et al., 1995). Therefore, the serum lipid levels (TC, LDL, VLDL, HDL and TGs) and glucose levels were estimated in this study as the marker of hyperlipidemia and hyperglycemia. HFD was induced for 10 weeks in the present study which lead to obesity and dyslipidemia as evidence by gain in body weight, increased feed intake (Kcal), BMI, Lee index and high lipid levels (Oldham, 2011). The present study was undertaken to determine the effect of ethanolic extract of *Cuscuta reflexa* extract on high fat diet induced obesity in Wistar rats and effect was compared with the standard drug Orlistat used in obesity and it was observed that *Cuscuta reflexa* extract has positive effect in the alteration of various parameters of obesity.

Obesity is a complex metabolic disorder with an excessive accumulation of fat in the body to an extent that it adversely affects the health of an individual (Retnasamy and Adikay, 2014). Numerous environmental factors predispose individuals to gain weight like freely available high-calorie food and sedentary life style (Bloom et al., 2008b). In modern medicine, there is great increase in the use of evidence based complimentary treatments like natural or herbal remedies in the management and prevention of obesity (Sharpe et al., 2007) common strategy being energy and diet restriction and adequate exercise. HFD has been used to develop experimental obesity characterized with dyslipidemia and insulin resistance in rodents (Woods et al., 2003). HFD fed rats exhibited significant increase in body weight, plasma glucose, triglycerides and total cholesterol level as compared to normal diet fed control rats (Srinavasan, 2005). The extent of metabolic disorder induced by the respective diet depends more on the specific rodent strains and the dietary regimen employed on the species itself e.g. C57BL/6J mice develop obesity (Almind et al., 2007), while 129S6 mice do not develop obesity (Surwit et al., 1988). The lipogenesis was up regulated by HFD in rats leading to elevation of plasma lipids (Storlien et al., 1991) characterized with elevated TG levels (Van Itallie, 2003), LDL-C levels (Van Itallie, 2003) and decreased serum HDL-C (Haslam and James, 2005; Glueek et al., 2001) in obese rats. There was increased fat accumulation due to impaired fat and glucose metabolism (Mopuri et al., 2015). HFD not only produced adipogenesis but also lead to metabolic diseases and chronic activation of inflammation (Tripathy et al., 2003). In the present study, treatment with *Cuscuta reflexa* extract attenuates the effect of HFD treatment.

Cuscuta reflexa, the giant dodder belonging to the family

Cuscutaceae, is a parasitic weed plant which has many traditional uses and possesses various pharmacological activities like anti-oxidant (Solat et al., 2013), antitumor (Dandopani et al., 2011), hepatoprotective (Jha and Shelke, 2011), antibacterial (Ayesha et al., 2011; Sharma et al., 2013), antiepileptic (Borole et al., 2011), hypoglycemic (Eram et al., 2002), anti-HIV (Mahmood et al., 1997), positive-inotropic (Singh and Garg, 1973), cardiotonic (Gilani and Aftab, 1992), spasmolytic (Prasad, 1965), free-radical scavenging, cholinergic (Kayath and Goel, 1995) and diuretic (Sharma et al., 2009) due to the presence of a wide range of phytochemical constituents (Anis et al., 1999; Kelker et al., 1984; Pacheco, 1966). Lupeol isolated from *Cuscuta reflexa* is a pharmacologically active tri-terpenoid and possesses antimicrobial, anti inflammatory, antitumor, antiprotozoal and chemoprotective properties (Gallo et al., 2009).

Cuscuta reflexa extract was given at the dose of 100 mg/kg and 200 mg/kg to HFD treated rats at the end of fourth week and continued up to the end of the tenth week with analysis of various anthropometric parameters. Several biochemical parameters were also determined. In present investigation it was observed that administration of *Cuscuta reflexa* extract in 100 mg/kg and 200 mg/kg dose for 6 weeks to the high fat diet fed animals significantly decreased the markers of obesity in both the doses as compared to HFD control group. The effect of 200 mg/kg dose was more significant as compared to 100 mg/kg dose. There was decrease in body weight, BMI, and Lee index of *Cuscuta reflexa* extract treated groups in dose dependent manner as compared to HFD treated rats. *Cuscuta reflexa* extract reduced food intake by hypophagic activity because obesity is associated with hyperphagia. An oral administration of HFD + Orlistat (30 mg/kg) and two doses of *Cuscuta reflexa* extract caused significant reduction in the level of serum lipids (TC, TG, VLDL, LDL) and glucose levels and the level of HDL got enhanced as compared to HFD fed group. *Cuscuta reflexa* extract decrease weight of adipose tissues: epididymal, mesenteric and retroperitoneal fat as compared to HFD. Studies have shown that Kaempferol and quercetin, constituents of *Cuscuta reflexa* significantly improves insulin-stimulated glucose uptake in mature 3T3-L1 adiopocytes. These two compounds of *Cuscuta reflexa* act at multiple targets to ameliorate hyperglycemia (Fang et al., 2008). The ethanolic extract of *Cuscuta reflexa* also showed antioxidant activity (Vijikumar, 2010) and significantly reduced the oxidative stress which was also evaluated by various in vitro studies (non-enzymatic hemoglobin glycolsylation). The decrease in $GABA_A$ activity in response to inhibition of 5-alpha reductase also prevents obesity (Patel et al., 2014b). The present study also implicates the more pronounced anti-obesity effects of 200 mg/kg dose as compared to 100 mg/kg dose of the extract. Hence, it has been observed that *Cuscuta reflexa* plays major beneficial role in obesity; and this study has provided a rational pharmacological basis for the use of *Cuscuta reflexa* in obesity.

5. Conclusion

On the basis of above discussion, it may be concluded that *Cuscuta reflexa* attenuated HFD-induced increase in the body weight, visceral adipose pad weights and Lee index, serum TC, TG and glucose levels. The anti-obesity activity of *Cuscuta reflexa* appears to be mediated by blocking DHT production; which decreases the accumulation of fats in the body by activation of $GABA_A$ receptor which tamps down signaling among neurons. Depression and anxiety also contribute to increase obesity. The high dose (200 mg/kg) of *Cuscuta reflexa* was found to be more effective as compared to its low dose (100 mg/kg). Hence these results evidently prove that *Cuscuta reflexa* can prevent the progression of obesity from predisposed factors and provided a rational pharmacological basis for the use of *Cuscuta reflexa* in obesity in man.

Conflicts of interest

The author declares no conflict of interest in preparing the present review.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.obmed.2019.02.001.

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