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Research article

ANTI-OBESITY EFFECT OF DEXTROMETHORPHAN IN HIGH FAT DIET INDUCED OBESITY IN RATS

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Abstract

Obesity is associated with significant comorbidities. Treatment options for obesity include only few drugs. Several hormones and receptors play key role in pathogenesis of obesity like NMDA, PPAR-gamma, leptin, pro-opiomelanocortin (POMC) and others. To check anti-obesity effect of Dextromethorphan (DXM) in high fat diet (HFD) induced obesity. Male Wistar albino rats (BW- 250-350 grams) were divided into 5 groups. Group 1 (Normal control) was fed with standard pellets. All the remaining groups were fed with High fat diet (HFD) to induce obesity. Group 2 served as HFD control. Group 3 (standard), group 4 (DXM-P) and group 5 (DXM-T) received orlistat (10 mg/kg, day 49 to 84), dextromethorphan (DXM) (15 mg/kg, day 0 to 84) and DXM (15 mg/kg, day 49 to 84) respectively. All the drugs were administered orally. Food intake (daily), water intake (daily) and body weight (weekly) were measured. Serum cholesterol (TC), Serum triglyceride (TG), HDL and LDL; OGTT, BMI, white adipose tissue (WAT) mass were measured. No significant difference was observed in food intake, BMI, TC, LDL and HDL between disease and treatment groups. BMI was significantly increased in HFD group and decreased in orlistat and DXM-P group. WAT mass and blood glucose were significantly decreased in all treatment groups as compared to HFD control. Administration of dextromethorphan in both the groups improved body weight, BMI (only DEX-P), WAT mass, glucose tolerance and serum TG. Dextromethorphan can be further studied for further development in treatment of obesity.

Key words: Obesity, Dextromethorphan, Orlistat, BMI

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Introduction

Obesity is serious health issue causing 2.8 M avoidable deaths each year. Obesity is characterized as an abnormal or excessive buildup of fat that poses a health concern. Obesity is defined as body mass index (BMI) greater than 30 **(1).** Comorbidities associated with obesity include increased risk of covid-19, cancers, hypertension, hypercholesteremia, type 2 diabetes, coronary heart disease, stroke, gallbladder disease, osteoarthritis, and dyspnea. Genetics, nutrition, imbalance between calory intake and exercise, eating habits, sedentary lifestyle, sleep, and stress contributes to excess weight and ultimately obesity. Mutations in FTO gene, hormonal disorders e. g hypothyroidism, insulin tolerance, menopause and polycystic ovary syndrome (PCOS), drugs (antidepressants, anticonvulsant, contraceptives, antipsychotics, and corticosteroids) may induce weight gain **(2, 3).** The prevalence of overweight and obesity in India is increasing faster than the world average. In Indian women, in year between 1998 and 2015, the prevalence of overweight and obesity increased from 8.4 to 15.5% and 2.2 to 5.1 % respectively. Study of global trends estimated that 27.8% of all Indians would be overweight and 5.0 % would be obese, by 2030 **(4).** The pharmacological treatment obesity includes FDA approved drugs like orlistat, phentermine-topiramate, naltrexone-bupropion, liraglutide, semaglutide and setmelanotide. The impact of these drugs in relation to the costs and benefits of therapy is always a topic for discussion **(5, 6).**

Obesity is associated with inflammation. Adipocytes secrete adipokines which play important roles in inflammation. These adipokines include TNF-α, leptin, resistin, visfatin, IL-6, and adiponectin. Obese individuals have adipose tissue that mainly secretes pro-inflammatory adipokines while lean individuals secrete anti-inflammatory adipokines. Chief adipokines include TNFs, interleukin (IL)- 6, leptin, angiotensin II, visfatin, and resistin. Anti-inflammatory adipokines include transforming growth factor-beta (TGF), IL- 4, IL- 10, IL- 13, IL- 1 receptor antagonist (IL- 1Ra), and adiponectin **(2).** Disturbances in gut microflora can lead to inflammation of the intestinal lining and ultimately obesity **(7).** Apart from this, peptide mediators, neurotransmitters of CNS and ANS, and hormones are also key players in orexigenic and anorexigenic pathways. Ghrelin, Cholecystokinin (CCK), Peptide tyrosine tyrosine (PYY), Pancreatic Polypeptide (PP), Glucagon-like peptide-1 (GLP-1), Neuropeptide-Y, insulin, leptin and Proopiomelanocortin (POMC) are few examples **(8).**

Two populations of neurons have mutually antagonistic functions found in arcuate hypothalamic nuclei (Arc) that control appetite and body weight. Activation of neuropeptide-Y (NPY)/agouti-related protein (AgRP) containing neurons results in increased food intake, while the activation of POMC neurons suppresses appetite. Almost all POMC containing neurons in Arc, also contain cocaine-and-amphetamine responsive transcript (CART), which serves as an anatomical marker and functions as an anorexigenic signal molecule. Within POMC neurons, α-MSH is the critical anorexigenic peptide produced by posttranslational of POMC. This centers further mediate higher centers such as limbic systems to further regulate the energy intake- energy expenditure homeostasis **(9, 10).** Activation of N-methyl-D-aspartate (NMDA) receptor regulates insulin sensitivity and lipid metabolism **(11).** The metabolite of dextromethorphan, 3-hydroxymorphinan, enhances mitochondrial biogenesis, browning and lipid accumulation in adipocytes via AMPK-dependent pathway. Activation of AMPK pathway by 3-hydroxymorphinan may be the potential target for obeisty **(12).** From all these literature review, we tried to find out possible anti-obesity effect of dextromethorphan in experimental obesity in rats using high fat diet (HFD).

Materials and methods

Drugs and Chemicals: Dextromethorphan hydrobromide was gifted from Lincoln phama, Ahmedabad). Orlistat (Eris life science limited); cholesterol and triglyceride kit (Span diagnostics Pvt Ltd., Surat, Gujrat, India) were purchased.

Ethics Approval: The project was approved by the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA) and the Institutional Animal Ethics Committee K. B. Institute of Pharmaceutical Education & Research, Gandhinagar; Project no. KBIPER/2022/646.

Animals and study groups: Healthy male Wistar albino rats (body weight 250 to 350 gms) were randomized based on body weight before the experiment started (on day 0). Animals were housed in polypropylene cage in controlled environment with a 22 °C temperature, 55± 5% humidity, and a 12 hr/12 hr alternated light/dark cycle. Animals had unlimited access to a standard laboratory feed (Pranav Agro, Baroda) and water *ad libitum.* Animals were divided into 5 groups each containing 6 animals. Normal control (Group 1) animals received standard diet. All the animals except Normal Control group were fed high fat diet (HFD) diet for 84 days to induce obesity **(13).** Disease control (HFD control-Group 2) animals received no treatment. Group 3 received orlistat (10 mg/kg, day 49 to 84). Animals in Group 4 (DEX-P) and group 5 (DXM-T) were administered

dextromethorphan (15 mg/kg) for prophylaxis (day 1 to 84) and as treatment (day 1 to 84) respectively. All the drugs were administered once in a day via per oral route.

Table 1: Study groups and treatments

Group No.	Group	Treatment	Duration
1	Control	Normal diet + Vehicle	Day 1 to 84
2	Disease control	HFD + Vehicle	Day 1 to 84
3	STD 1	HFD + Orlistat (10 mg/kg, PO, OD)	Day 49 to 84
4	Test 1 (DEX-P)	HFD + Dextromethorphan (15 mg/kg, PO, OD)	Day 1 to 84
5	Test 2 (DXM-T)	HFD + Dextromethorphan (15 mg/kg, PO, OD)	Day 49 to 84

Parameters: Food intake (daily) and body weight (weakly) were measured from day 1 to 84. Serum total cholesterol (TC), serum triglyceride (TG), LDL and HDL (on day 28, 49, 63, 84) was measured. Oral glucose tolerance test (OGTT) performed on day 35 and 70 using glucometer. On day 84, all the animals were sacrificed using isoflurane inhalation anesthesia. Epididymal white adipose tissue (WAT) was isolated and weighed. BMI was calculated on day o and 84.

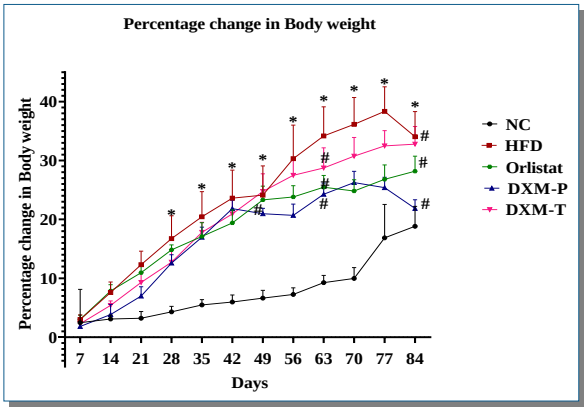
Statistical Analysis: Data was expressed as the mean ± SEM. One-way ANOVA multiple comparison test followed by post hoc Tuckey test was performed for quantitative parameters (Lipid parameters, body weight, OGTT, WAT mass). For food intake, Two-way ANOVA followed by Bonferroni test was performed. $p<0.05$ was considered as statistical significance. Statistical software: Graph-pad Prism version 9.0 (free trial version)

Results

Percentage change in Body weight:

Animals in HFD group (20.5±4.3, 23.6±4.8, 24.13±4.9, 30.3±5.7, 34.2±4.9, 36.1±4.6, 38.3±4.2, 34.0±4.3) showed significant change (increase) in percentage body weight as compared to NC group (5.5±0.9, 5.9±1.2, 6.7±1.3, 7.3±1.1, 9.3±1.9, 16.9±5.7, 18.82±3.4) on day 35, 42, 49, 56, 63, 70, 77 and 84 respectively. Treatment with DXM-P significantly changed (decreased) percentage body weight on day 49, 63 and 84 (20.9±0.9, 20.4±1.9, 21.9±1.5) as compared to HFD group. Orlistat treatment and DXM-T significantly decreased percentage body weight (25.5±1.9, 28.2±0.54) and (28.7±3.4, 32.8±2.9) on day 63 and 84 as compared to HFD group respectively **(Figure 1).**

Figure 1: Effect of DXM on Percentage change in Body weight

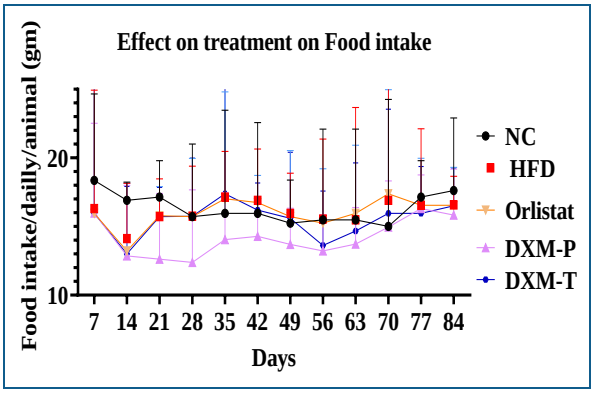


*Indicates significant difference from control group; #Indicates significant difference from HFD group ($p<0.05$, One way ANOVA followed by Tukey's test)

Food intake

Intake was expressed as cumulative food intake gm/animal/day. There was no significant difference in food intake between HFD group and NC group was observed **(Figure 2).**

Figure 2: Effect of DXM on Food intake



$p<0.05$, Two-way ANOVA followed by Bonferroni test

BMI

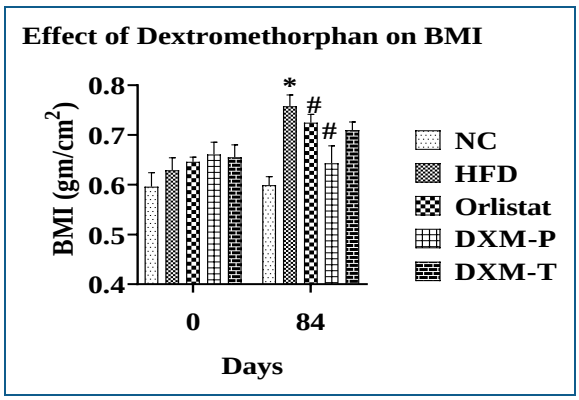
BMI was significantly higher in HFD group (0.59 ± 0.01) as compared to NC group (0.59 ± 0.01) on day 84. Orlistat (0.72 ±.016), DXM-P (0.64±0.03) showed significantly decreased BMI as compared to HFD group. Treatment group DXM-T did not show any significant change in BMI on day 84 **(Figure 3).**

Oral glucose tolerance test (Day 35)

Blood glucose was significantly higher in HFD group (133.2± 2.2) as compared to NC group (115± 3.4) (at 60 min). Significant decrease in blood glucose was

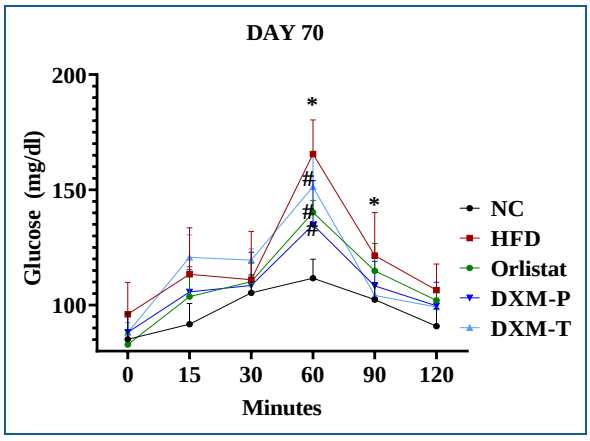
found in DXM-P (128±4.2) as compared to HFD group (at 60 min) **(Figure 4).**

Figure 3: Effect of DXM on Body Mass Index (BMI)



*Indicates significant difference from control group; #Indicates significant difference from HFD group (p<0.05, One way ANOVA followed by Tukey's test)

Figure 4: Oral glucose tolerance test (Day 35)



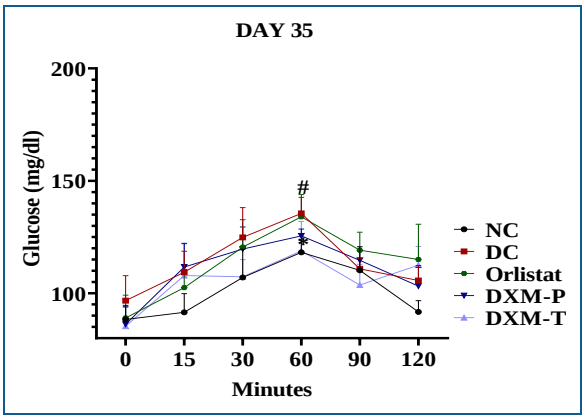
Oral glucose tolerance test (Day 70)

Blood glucose was significantly higher in HFD group (145.2± 2.2, 170±3.4) as compared to NC group (100± 3.3, 110±2.6) (at 60 and 90 min). The significant difference in blood glucose was found in orlistat (145.2±2.4), DXM-P (138.7±3.2), DXM-T (159.3±4.2) as compared to HFD group (at 60 min) **(Fig. 5).**

Effect of DXM on serum TC, HDL, LDL and TG

No significant difference was observed in serum TC, HDL, and LDL between HFD group and NC group. Serum triglyceride was significantly increased in HFD group (175.7±14.2, 189.9±10.6) as compared NC group (143±1.6, 141.3±7.4) on day 63 and 84 respectively. Orlistat (147.6± 13.07), DXM-P (143.2±11.6) and DXM-T (163± 12.8) significantly decreased serum TG level compared to HFD on day 84 respectively **(Table 2).**

Figure 5: Oral glucose tolerance test (Day 70)

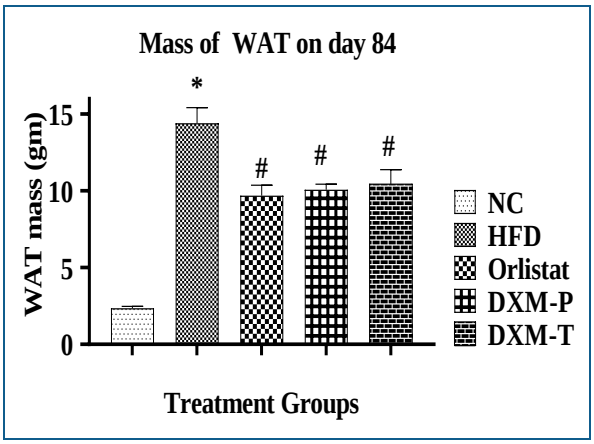


*Indicates significant difference from control group; #Indicates significant difference from HFD group (p<0.05, One way ANOVA followed by Tukey's test)

White adipose tissue (WAT) mass

Animals in HFD group (13.7 ± 0.96) had significantly higher WAT mass as compared to NC group (2.4 ±.012) on day 84. Animals treated with Orlistat (0.72 ± 0.02), DXM-P (0.64 ± 0.035), DXM-T (0.71 ± 0.02) showed significantly lower WAT mass as compared to HFD group **(Figure 6).**

Figure 6: Effect of DXM on Mass of white adipose tissue (WAT)



*Indicates significant difference from control group; #Indicates significant difference from HFD group (p<0.05, One way ANOVA followed by Tukey's test)

Table 2: Effect of DXM on Serum TC, HDL, LDL and TG

Lipid Parameters	DAY	NC	HFD	Orlistat	DXM-P	DXM-T
TC (mg/dL)	28	115.1±3.6	122.4±3.6	117.4± 5.7	16.2 ± 19.8	128.3 ± 5.8
	49	131.4±16.3	131.3±16.3	104.0±10.5	116.3±8.5	119.2±8.9
	63	123.9± 6.8	123.9±6.8	111.1 ± 4.0	122.9 ± 9.7	132.5 ± 9.7
	84	43.21 ± 5.3	143.2±5.3	115.4± 7.0	128.27 ± 5.8	120.5 ± 8.0
HDL (mg/dL)	28	45.7±0.97	43.6±1.3	43.08±2.2	44.51±2.6	41.93±1.3
	49	46.6±2.3	40.1±1.2	41.18±1.3	47.83±1.8	40.91±0.3
	63	44.7±0.24	40.2±1.2	43.28±1.4	47.83±1.9	44.81±1.0
	84	43.3±3.4	40.51±3.1	39.92±1.5	41.38±1.6	42.04±1.2
LDL (mg/dL)	28	45.6±4.5	54.1±5.4	48.3±48.1	48.1±19.8	56.7±5.3
	49	42.2±2.2	61.0±16.7	31.5±47.1	47.1±7.9	46.1±8.7
	63	38.2±2.9	45.3±6.5	37.1±45.6	45.6±7.8	58.6±6.8
	84	43.3±3.4	64.7±4.1	45.9±58.2	58.24±5.6	45.7±7.5
TG (mg/dL)	28	120.8 ± 1.8	123.5 ± 8.5	129.8 ± 9.6	118.0 ± 3.9	123.37 ± 5.2
	49	131.1±2.2	151.3±6.2	156.8±9.1	136.4±9.1	123.4 ± 5.3
	63	143.0±1.6	175.7 ±14.2*	153.7 ±11.2	147± 13.4	145.3 ± 10.1
	84	141.3±7.4	189.9 ±10.5*	147.6± 13.1#	143.2 ±11.6#	164.3 ±12.8#

*Indicates significant difference from control group
#Indicates significant difference from HFD group ($p<0.05$, One way ANOVA followed by Tukey's test)

Discussion

Administration of HFD for 84 days induced obesity in HFD rats. This was demonstrated by increase body weight and BMI. Body mass index is a widely used surrogate marker of obesity. Treatment with orlistat, DXM- P and DXM-T in rats did not show increase in % body weight as compared to HFD group. In the current study, feeding HFD for 84 days resulted in considerably higher serum TG levels in the HFD rats, but there was no significant change in TC, LDL and HDL levels. No significant difference was observed in orlistat group, DXM-P and DXM-T group.

Administration of glucose during OGTT in HFD group significantly increased glucose level on day 35 (at 60 minute) and on day 70 (at 60 and 90 minute), indicating glucose intolerance. Administration of dextromethorphan significantly improved glucose tolerance on day 70 when administered from day 49. Prophylactic administration of dextromethorphan improved glucose tolerance on both day 35 and 70. Obesity is frequently associated with glucose intolerance indicated as impaired OGTT **(14).** BMI was measured on day 0 and 84. HFD treated rats showed significantly higher BMI compared to control animals. Orlistat and prophylactic administration of dextromethorphan in DXM-P group significantly decreased BMI. Epididymal WAT mass of HFD treated animals was significantly higher than normal animals.

All animals receiving Orlistat, DXM-P and DXM-T showed significantly lower WAT mass value as compared to HFD animals. In our study, DEX-P and DEX-T did not alter lipid parameters except serum TG. This can be justified by numerous studies that show obese people may not have always hypercholesteremia. The prevalence of glucose intolerance was found to be higher in children and adolescents with severe obesity **(15).** Obesity is strongly correlated with insulin impairment and glucose intolerance **(16).** Out study also showed the same. The obese rats showed impaired glucose tolerance. Dextromethorphan treatment improved glucose tolerance probably due to improving insulin-leptin sensitivity at central level. Hypothalamic POMC neurons play important role in obesity **(17).**

Mutations of POMC are associated with obesity phenotypes. It has been reported that mouse knockouts for POMC, MC4R AND MC3R expressed as obese phenotype. Mutations of POMC and MC4R in humans results into same results. POMC neurons release α-melanocyte-stimulating hormone (α-MSH) which

binds to melanocortin-4 receptor (MC4R) expressed by MC4R neurons to the paraventricular nucleus (PVN). This ultimately results into decreased energy intake **(18).** Dextromethorphan by its action on POMC, AgRP/NPY, and MC4R neurons pathway, improves body weight and fat deposition.

Conclusion

Dextromethorphan decreases the body weight, BMI and adipose tissue mass; improves glucose tolerance in obese rats demonstrating its promising role in obesity.

Financial disclosure statement

Study was supported by KBIPER, Gandhinagar

Conflicts of interest

None declared.

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