# Effects of Curcumin and Telmisartan on Olanzapine and high fructose diet induced Metabolic Syndrome in Sprague Dawly Rats

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## ABSTRACT

**Objective:** To study the effects of curcumin and telmisartan on olanzapine, high fructose diet (HFD) and both olanzapine and HFD-induced metabolic syndrome. **Method:** Adult male Sprague Dawly (SD) rats were used for the study. Animals were divided into ten groups including normal and HFD controls. The obesity/metabolic syndrome was induced using olanzapine (1 mg/kg; *i.p.*), a second generation antipsychotic and HFD. Effect of curcumin (50 mg/kg; *p.o.*) and telmisartan (5 mg/kg; *p.o.*) on olanzapine, HFD and both olanzapine and HFD-induced metabolic syndrome. All drugs were administered for 28 days. The blood sample was collected through retro orbital sinus and the plasma was separated at the end of study. The plasma sample was used to estimate the biochemical parameters such as blood glucose, aspartate aminotransferase (ALT), alanine aminotransferase (ALT), urea, uric acid, creatinine, total cholesterol, triglyceride; and high-density lipoprotein (HDL) levels were analyzed and the low-density lipoprotein (LDL) levels were calculated using Frieldwann's equation. After completing the experiment, all experimental animals were sacrificed by cervical dislocation and their organs such as heart, liver, kidney and peritoneal fat pads were removed and the absolute organ weight was measured. **Result:** The animals treated with olanzapine and fed with HFD showed significant increase in body weight and biochemical parameters when compared to the control group. Curcumin and telmisartan were significantly ($P$<0.001) inhibited, the HFD and olanzapine induced increase in body weight and also brought the biochemical levels to normal when compared to the olanzapine and HFD groups, respectively. The animals treated with telmisartan showed significant inhibition on the liver weight and peritoneal fat levels when compared to control group. **Conclusion:** The study results suggested that curcumin and telmisartan significantly inhibited the olanzapine and HFD-induced metabolic syndrome. Telmisartan affects the total lipid profile, glucose metabolism and decreases the body weight.

**Keywords:** curcumin, metabolic syndrome, telmisartan, olanzapine.

## INTRODUCTION

Antipsychotic agents are one of the most commonly used drugs to calm/sedate, control the symptoms of mania and relieve acute positive symptoms of schizophrenia, etc. in the 21st century. The most common adverse effect observed in antipsychotic drug therapy is rapid weight gain that is causing obesity and other metabolic syndromes. From past evidence we know that patients treated with 2nd generation antipsychotic drugs for a long term showed significant weight gain.[1,2]

Olanzapine is an atypical antipsychotic, approved by Food and Drug Administration (FDA) for the treatment of schizophrenia and bipolar disorder. It is structurally similar to clozapine, but is classified as a thienobenzodiazepine.[3] Long term administration of olanzapine is associated with high weight gain. Weight gain especially when manifested as intra-abdominal obesity, is a significant long term health issue as it is associated with insulin resistance and resultant metabolic effects such as elevated triglycerides, diabetes and hypertension, all of which increase cardiovascular

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diseases.[4,5] Olanzapine administration causes increase in ghrehlin which is responsible for increase in body weight.[6] Patients with schizophrenia often have immediate concerns regarding weight gain and poor physical function, discomfort in public places, poor self-esteem and problems with sexual performance. Increase in body weight may cause metabolic syndrome such as insulin resistance, hypoinsulinamia, glucose intolerance, adipogenesis, dyslipidemia and hypertension.[7,8] Like olanzapine, high fructose diet (HFD) also causes insulin resistance, hypertension, hepatic stress and weight gain.[9,10,11,12] Curcumin and telmisartan are a natural anti-oxidant and angiotensin II receptor antagonist, respectively. The anti-obesity and insulin resistant properties of this compound have already been proved.[13,14] Hence, the present study was planned to determine and compare the effect of curcumin and telmisartan on both olanzapine and HFD-induced metabolic syndrome.

## MATERIALS AND METHODS

### Animals

Experimental study was carried out using adult male Sprague Dawly (SD) rats weighing between 140-160 g. The animals were housed in clean, hygienic and large polypropylene cages. Animals were acclimatized to light and temperature with a 12h-12h dark-light cycle. The rats were fed with normal rodent pellet diet and water *ad libitum*. The rat pellets were supplied by M/s. Hindustan Lever Ltd., Bangalore, India. During the course of the experiments, the respective HFD-fed animal groups received HFD diet. The study protocol was approved by the Institute Animals Ethics Committee (IAEC/NCP/40/10), and all animal experiments were carried out in accordance with the guidelines of the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA), India.

### Metabolic syndrome inducing agents

High fructose diet (HFD) containing fructose 624 g/kg (62%), fats as vegetable oils 5 g/kg, protein 223 g/kg (22%), necessary amino acids, vitamins 1.25% and minerals.[15,16] Olanzapine (t.i.d) at a dose range of 0.5-2.0 m/kg mimics the clinical features in animals such as weight gain associated with hyperphagia, enhanced feeding efficiency, adiposity and altered locomotor activity and satiety signaling in 14 days.[10,17] In the present study, 1mg/kg olanzapine (o.i.d) was used for a duration of 28 days to induce obesity in SD rats.

### Effects of curcumin and telmisartan on olanzapine and HFD induced metabolic syndrome

Induction of insulin resistance in the experimental animals was carried out by feeding HFD. The animals were divided into the 10 groups, each comprising six animals as follows:

Group I : Control (fed with normal diet chows)
Group II : High fructose diet (HFD) control
Group III : Olanzapine (1 mg/kg)
Group IV : HFD + Olanzapine 1 mg/kg
Group V : HFD + Curcumin 50 mg/kg
Group VI : Olanzapine 1 mg/kg + Curcumin 50 mg/kg
Group VII : HFD + Olanzapine 1 mg/kg + Curcumin 50 mg/kg
Group VIII : HFD + telmisartan 5 mg/kg
Group IX : Olanzapine + Telmisartan 5 mg/kg
Group X : HFD + Olanzapine 1 mg/kg + Telmisartan 5 mg/kg

Curcumin (50 mg/kg b.wt) and telmisartan (5 mg/kg b.wt) doses were used for this study.[18,19] The standard drug and investigational produces were administered orally for 28 days. The metabolic syndrome was induced by treating/feeding the experimental animals with olanzapine or HFD. Olanzapine was administered during mornings and all other investigational products were administered during afternoon timings. During the study period, the weekly body weight variation was determined. The animals were fasted for 24h and the blood sample was collected through retro orbital sinus at the end of the study.[20] The blood samples were collected in sodium ethylenediaminetetraacetic acid (EDTA) tubes, centrifuged at 3000 RPM for 20 min and subjected to biochemical analysis (Vital Scientific N.V., The Netherlands). Plasma samples were used to estimate the biochemical parameters such as blood glucose, AST, ALT, urea, uric acid, creatinine, total cholesterol, triglyceride and HDL levels. The lipid profile, liver enzyme profile and glucose levels were estimated using Randox (E-merk India Ltd.) and Lab kit enzymatic kits, respectively. The LDL levels were calculated using Frieldwann's equation.[21,22] At the end of the study, all experimental animals were sacrificed by cervical dislocation[23] and organs such as heart, liver, kidney and peritoneal fat pads were removed and the absolute organ weight was measured and relative organ weight was calculated.

### Statistical Analysis

The mean and standard error of mean (SEM) values were calculated for each parameter. Significant differences between the groups were determined using repeated Analysis of Variance (ANOVA) measures followed by Dunnett's test. A $P$ value less than 0.05 was considered significant.

## RESULT

Effect of telmisartan and curcumin on body weight in HFD and olanzapine-induced metabolic dysfunction in rats is presented in Table 1. The HFD, olanzapine and both HFD

and olanzapine administered groups showed a significant ($P<0.001$) increase in body weight when compared to the control group at the end of the study. At the same time, curcumin and telmisartan significantly ($P<0.001$) inhibited HFD and olanzapine induced increase in body weight when compared to the HFD-fed animals and olanzapine administered group. Olanzapine, HFD + olanzapine and HFD + olanzapine + telmisartan treated groups significantly increased the relative organ weight of liver ($P<0.05$). Like HFD, olanzapine and HFD + olanzapine treated animals showed significant increase in the peritoneal fat levels when compared to the control ($P<0.01$). Telmisartan in HFD treated animals, showed significant inhibition on the liver weight. In telmisartan treated animals, marked changes in reduction in peritoneal fat levels were observed, but it was not statistically significant (when compared to control group).

Effect of curcumin and telmisartan on biochemical and lipid profiles is presented in Tables 2 and 3. HFD, olanzapine and HFD and olanzapine combined groups showed

**Table 1: Effect of curcumin and telmisartan on absolute body weight and relative organ weight in olanzapine and HFD induced insulin metabolic syndrome**

| Groups | Absolute body weight | Relative organ weight | | | |
|---|---|---|---|---|---|
| | | Heart | Liver | Kidney | Peritoneal fat |
| Group-I | 192.33 ± 1.73 | 0.32 ± 0.01 | 2.38 ± 0.08 | 0.67 ± 0.01 | 0.70 ± 0.02 |
| Group-II | 284.50 ± 3.18*** | 0.36 ± 0.01 | 2.42 ± 0.02 | 0.65 ± 0.01 | 1.46 ± 0.05** |
| Group-III | 234.17 ± 1.92*** | 0.34 ± 0.01 | 3.00 ± 0.15** | 0.67 ± 0.05 | 1.28 ± 0.05** |
| Group-IV | 305.50 ± 2.09*** | 0.36 ± 0.02 | 3.12 ± 0.11** | 0.65 ± 0.02 | 1.54 ± 0.06** |
| Group-V | 215.67 ± 3.84&&& | 0.31 ± 0.02 | 2.27 ± 0.06 | 0.66 ± 0.02 | 0.71 ± 0.06 |
| Group-VI | 192.83 ± 1.58### | 0.34 ± 0.02 | 2.39 ± 0.06 | 0.68 ± 0.04 | 0.67 ± 0.10 |
| Group-VII | 197.67 ± 2.14$$$ | 0.38 ± 0.02 | 2.41 ± 0.05 | 0.61 ± 0.03 | 0.97 ± 0.09 |
| Group-VIII | 183.33 ± 2.36&&& | 0.31 ± 0.01 | 1.79 ± 0.06** | 0.69 ± 0.02 | 0.62 ± 0.14 |
| Group-IX | 179.17 ± 1.49### | 0.36 ± 0.02 | 2.11 ± 0.07 | 0.65 ± 0.01 | 0.62 ± 0.05 |
| Group-X | 172.83 ± 1.82$$$ | 0.37 ± 0.01 | 2.12 ± 0.05 | 0.66 ± 0.02 | 0.62 ± 0.04 |

Values are mean ± SEM (N=6). *$P$<0.05; **$P$<0.01; ***$P$<0.001 as compare to control; &&&$P$<0.001 as compare to HFD; ###$P$<0.001 as compare to olanzapine; $$$$P$<0.001 as compare to olanzapine + HFD. One way ANOVA followed by Dunnett's multiple comparison tests.

**Table 2: Effect of curcumin and telmisartan on lipid profile in olanzapine and HFD-induced insulin resistance and metabolic syndrome**

| Groups | Total cholesterol | Triglycerides | HDL Levels | LDL levels |
|---|---|---|---|---|
| Group-I | 56.167 ± 1.662 | 74 ± 1.983 | 33.3 ± 0.766 | 25.667 ± 1.174 |
| Group-II | 74.833. ± 1.493*** | 143.333 ± 2.108*** | 24.333 ± 1.054*** | 31.162 ± 1.078** |
| Group-III | 65.667 ± 1.282** | 111.833 ± 2.400*** | 20.66 7 ± 1.145*** | 31.667 ± 1.606*** |
| Group-IV | 85.167 ± 1.537*** | 171.667 ± 3.169*** | 15.333 ± 0.989*** | 36 ± 0.775*** |
| Group-V | 46.833 ± 3.106&&& | 82.833 ± 1.60&&& | 34.5 ± 0.99&&& | 21.333 ± 0.80&&& |
| Group-VI | 47.667 ± 0.84### | 64.167 ± 1.76### | 34.5 ± 0.96### | 20.167 ± 0.70### |
| Group-VII | 68.167 ± 1.17$$$ | 103.833 ± 1.33$$$ | 24.333 ± 1.12$$$ | 21.667 ± 0.99$$$ |
| Group-VIII | 46.667 ± 1.783&&& | 64.833 ± 1.33&&& | 35.5 ± 0.67&&& | 20.333 ± 0.62&&& |
| Group-IX | 43.5 ± 0.89### | 64.667 ± 1.54### | 36.833 ± 0.83### | 18 ± 1.06### |
| Group-X | 63.167 ± 1.40$$$ | 88 ± 2.08$$$ | 35 ± 0.52$$$ | 20.5 ± 0.43$$$ |

Values are mean ± SEM (N=6). **$P$<0.01, ***$P$<0.001 as compare to control; &&&$P$<0.001 as compare to HFD; ###$P$<0.001 as compare to olanzapine; $$$$P$<0.001 as compare to olanzapine + HFD. One way ANOVA followed by Dunnett's multiple comparison tests.

**Table 3: Effect of curcumin and telmisartan on biochemical parameters in olanzapine and HFD induced insulin resistance and metabolic syndrome**

| Groups | Blood glucose | AST | ALT | Urea | Uric acid | Creatinine |
|---|---|---|---|---|---|---|
| Group-I | 91.00 ± 1.32 | 22.66 ± 0.62 | 33.66 ± 0.96 | 32.33 ± 0.33 | 1.65 ± 0.03 | 0.83 ± 0.06 |
| Group-II | 158.33 ± 1.23*** | 80.16 ± 0.65*** | 84.33 ± 1.05*** | 43.83 ± 0.70*** | 4.71 ± 0.04*** | 2.27 ± 0.08*** |
| Group-III | 138.66 ± 1.69*** | 86.00 ± 1.18*** | 90.17 ± 1.07*** | 37.83 ± 0.48*** | 3.40 ± 0.06*** | 1.62 ± 0.05*** |
| Group-IV | 177.16 ± 1.67*** | 96.16 ± 1.01*** | 102.0 ± 0.97*** | 46.66 ± 0.67*** | 6.68 ± 0.09*** | 4.25 ± 0.09*** |
| Group-V | 114.66 ± 1.63&&& | 43.33 ± 0.72&&& | 52.66 ± 0.96&&& | 37.33 ± 0.49&&& | 2.72 ± 0.10&&& | 1.52 ± 0.06&&& |
| Group-VI | 108.00 ± 1.16### | 36.16 ± 0.79### | 44.83 ± 1.12### | 40.83 ± 0.91## | 2.65 ± 0.09### | 1.09 ± 0.06### |
| Group-VII | 123.00 ± 2.21$$$ | 42.66 ± 0.88$$$ | 51.67 ± 0.72$$$ | 46.17 ± 0.65$$$ | 3.42 ± 0.10$$$ | 2.16 ± 0.07$$$ |
| Group-VIII | 109.50 ± 3.13&&& | 52.83 ± 0.87&&& | 62.50 ± 0.99&&& | 33.33 ± 0.84&&& | 2.22 ± 0.06&&& | 1.45 ± 0.12&&& |
| Group-IX | 108.16 ± 3.27### | 43.33 ± 0.66### | 52.83 ± 0.54### | 36.50 ± 0.43 | 1.53 ± 0.08### | 0.88 ± 0.06### |
| Group-X | 123.00 ± 1.98$$$ | 47.16 ± 0.79$$$ | 60.50 ± 0.85$$$ | 34.0 ± 0.36$$$ | 2.20 ± 0.06$$$ | 1.27 ± 0.06$$$ |

Values are mean ± SEM (N=6). ***$P$<0.001 as compare to control; &&&$P$<0.001 as compare to HFD; ##$P$<0.01, ###$P$<0.001 as compare to olanzapine; $$$$P$<0.001 as compare to olanzapine + HFD. One way ANOVA followed by Dunnett's multiple comparison tests.

a significant increase in blood glucose levels, AST, ALT, urea, uric acid, creatinine and lipid profile when compared to the control group. Curcumin and telmisartan significantly inhibited the HFD and olanzapine induced biochemical changes when compared to the HFD group and olanzapine, respectively. Like the HFD and olanzapine + curcumin combined group, the HFD and olanzapine + telmisartan combined group also significantly ($P<0.001$) inhibited the biochemical changes when compared to the HFD-fed group.

## DISCUSSION

The present study shows that treatment with curcumin and telmisartan prevents increase in body weight response to olanzapine and HFD-induced weight gain in rats. This suggests curcumin and telmisartan inhibited the olanzapine and HFD effects on body weight. According to our study results, it is possible to attenuate that antipsychotic-induced weight gain in SD rats was inhibited by ACE inhibitors and curcumin, a natural antioxidant.

The rats fed with normal diet did not exhibit excessive gain in body weight, but HFD-fed and olanzapine-administered animals showed significant increase in body weight. Shertzer et al. reported olanzapine-induced metabolic toxicity and the study report concludes that the olanzapine-induced weight gain was inhibited by the analgesic acetaminophen and by the antioxidant tetrahydroindenoindole.[24] A possible explanation for this finding may be found in previous studies where weight gain in humans and rodents treated with olanzapine was associated with single nucleotide polymorphisms (SNPs) in genes related to peripheral lipid homeostasis. In this way, the lipid deposing in adipose tissue may be proportional to the amount of fat consumption.[24,25] Like antioxidants, curcumin also acts on oxidative stress pathway and alters the disease state.

The animals treated with olanzapine and HFD showed significant increase in lipid levels suggesting that the olanzapine/second generation antipsychotic agents are the risk factors for hyperlipidemia and other cardiovascular diseases.[1] Olanzapine alone and olanzapine + HFD increased the triglyceride levels. It is a well known fact that olanzapine increases the body weight and serum triglyceride levels, as proved by various studies.[26] In telmisartan group, significant decrease in the relative organ weight of liver may be due to the reducing accumulation of visceral fat and decreased adipocyte size.[27]

Telmisartan is a known angiotensin II receptor antagonist that has partially agonistic properties on peroxisome proliferator-activated receptor (PPAR-γ).[28] The effects of telmisartan on insulin resistance and weight gain in genetic and nongenetic animal models was already reported. The earlier reports on effects of telmisartan on pioglitazone-induced increase in fat mass was modest in the SD rats and Zucker rats suggested that telmisartan did not interfere with the insulin-sensitizing properties of pioglitazone and attenuated the glitazone-induced increase in fat mass.[13]

In some cases, olanzapine caused metabolic syndrome by Pro12Ala polymorphism of PPAR-gamma2 and the polymorphism of PPAR might be important in olanzapine-induced weight gain.[29] High fructose feeding also altered lipid metabolism and decreased insulin sensitivity by suppression of hepatic PPAR-α.[30] The agent acting on the PPAR-γ receptor level needs to address the olanzapine and HFD-induced metabolic syndrome. Along with second generation antipsychotic drug treatment, addition of the natural antioxidant curcumin or partial PPAR-γ agonist telmisartan may helpful in controlling the olanzapine induced polymorphism on peroxisome proliferator-activated receptor to some extent. Thereby, the olanzapine/HFD metabolic syndrome/disease state will be altered.

The second generation antipsychotic drugs including olanzapine cause weight gain and obesity-related diseases result from excessive food intake and fat consumption. However, the rats were fed with HFD and treated with olanzapine mediated metabolic disorders, in part by altering the oxidative stress pathway. Curcumin is well known anti-oxidant, that may partially act as an uncoupling agent to increase the basal metabolism rate, thus reducing body weight gain and fat deposition.[24]

## CONCLUSION

The investigation was undertaken to study the effects of Curcumin and Telmisartan on olanzapine and HFD-fed induced insulin resistance. Thus, our results indicate curcumin and telmisartan affects the total lipid profile and glucose metabolism and favors the improvement of blood glucose and lipid profile. It also decreases body weight adipogenesis in liver. Further studies are needed to explore the underlying mechanisms.

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