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Original Article

Hesperidin Attenuate Olanzapine-Induced Weight Gain, Dysregulation of Lipid and Glucose Metabolism in Rats

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ABSTRACT

Background: Olanzapine causes alterations in lipid and glucose metabolism, indicated by weight gain, and altered metabolic profiles. Hesperidin has been related to numerous positive health benefits including improvements in cardiovascular and metabolic function making it a potentially suitable candidate to counteract the negative effects of olanzapine treatment. Hence the purpose of the study is to investigate the effect of hesperidin on olanzapine-induced weight gain, and associated lipid and glucose metabolic dysfunctions in female Sprague Dawley rats. **Materials and Methods:** Olanzapine (2 mg/kg *b.i.d. i.p.)* was administered for 28 days to induce weight gain, dyslipidemia and insulin resistance in rats. Hesperidin was tested at doses of 50, 100, 200 mg/kg *p.o.* over 28 days. Body weight, food intake, and water intake were noted daily. Locomotor activity was recorded weekly. Novel object recognition test, Oral glucose tolerance test, and Homeostatic Model Assessment for Insulin Resistance and antioxidant biomarkers were measured followed by histopathological examination. **Results and Discussion:** Treatment with hesperidin notably reduced the weight gain and hyperphagia brought on by olanzapine administration. Significant improvement in locomotor activity was observed upon hesperidin administration. Further, hesperidin resulted in a significant improvement in the discrimination ratio in the Novel object recognition test. Administration of hesperidin significantly reduced the glucose intolerance, insulin resistance and dyslipidemia induced by olanzapine treatment. Furthermore, leptin and adiponectin levels were significantly improved upon hesperidin administration. Additionally, there was a significant improvement in anti-oxidant biomarkers followed by amelioration of histological examination. **Conclusion:** In conclusion, it was found that hesperidin reduced weight gain, and improved lipid, and glucose dysregulation caused by olanzapine administration. Additionally, it mitigates olanzapine-induced changes in plasma levels of leptin, and adiponectin. Hesperidin also improved cognitive behavior in olanzapine-treated rats.

Keywords: Olanzapine, Weight gain, Dyslipidemia, Insulin resistance, Leptin.

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INTRODUCTION

Obesity is a multifactorial disorder that majorly contributes to public health issues since it can lead to several metabolic and cardiovascular problems as well as reduced quality of life.[1] The WHO estimates that 39% of adults were overweight in 2016 and 13% were obese, and by 2020, 39 million children will be overweight or obese.[2] Various factors involved in the development of obesity include dietary habits, lifestyle, genetic, and environmental factors.[1] Additionally, certain medications such as antipsychotics are highly linked with increased weight, and other metabolic disorders in patients.[3] Olanzapine is one of the most efficacious atypical anti-psychotics used to treat schizophrenia and bipolar disorders. Administration of olanzapine demonstrates the alteration of metabolic profiles which is evident by weight gain, and changes in lipid and glucose metabolism.[4,5] Significant weight gain with olanzapine has been reported in various clinical as well as preclinical studies.[6-8] Further it stimulates appetite by interfering with the neurotransmitter systems that control satiety and hunger, which results in an excessive intake of calories. Additionally, the medication alters glucose and lipid metabolism, leads to insulin resistance, and disturbs metabolic homeostasis.[5] Olanzapine also affects adipose tissue by promoting fat accumulation and preventing fat breakdown.[9] Hormonal imbalances for instance elevated leptin levels results in increased appetite and weight gain. Olanzapine-induced sedation and decreased physical activity may also lower energy expenditure.[10]

Over the years, many researchers have directed their efforts in this area to understand the mechanism of olanzapine-induced weight gain, and to find an effective intervention to mitigate

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these unwanted side effects The seek for adjuvant therapy for the olanzapine treatment has led to the exploration of natural substances with possible anti-obesity properties. Flavonoids are highly reported for their efficacy on metabolic disorders including obesity as a potential therapeutic adjuvant.[11,12]

Hesperidin is a bioflavonoid, present in various citrus fruit like lemon, orange, grapefruit, tangerine etc;[13] reported to possess anti-hyperlipidemic, cardioprotective, anti-diabetic, anti-hypertensive, antioxidant and anti-inflammatory properties[14-17] making it a potentially suitable candidate to overcome olanzapine-induced metabolic disturbances. In preclinical research, animal models play a pivotal role to understand the underlying mechanism for olanzapine-induced obesity to identify beneficial treatment strategies.

Hence, we aim to investigate the complex interaction between olanzapine administration and weight gain as well as to explore the possible therapeutic benefits of hesperidin as a therapeutic approach in female SD rats. Understanding the mechanisms of olanzapine-induced obesity and exploring the efficacy of hesperidin to counteract the effects of olanzapine-induced obesity, could contribute towards the development of novel approaches to manage weight gain and other related metabolic disturbances associated with antipsychotic medication.

MATERIALS AND METHODS

Animals and Ethical Clearance

The IAEC of KLE College of Pharmacy, Belagavi granted ethical clearance for the animal investigations bearing resolution no. (KLECOP/CPCSEA-Reg.No.221/Po/Re/S/2000/CPCSEA, resolution no. 30). The animals were obtained from a vendor, registered at CPCSEA and were kept in a pathogen-free setting. The animals were subjected to a 12 hr cycle of light and dark, during the study.

Study Design

Female SD rats (180±10 g) were randomly divided into 5 groups, containing 6 animals in each group. These groups were (i) Normal: receive vehicle, (ii) Olz: receive olanzapine 2 mg/kg *b.i.d, i.p.*;[18] (iii) Olz+H50: receive olanzapine 2 mg/kg *b.i.d, i.p.*+Hesperidin 50 mg/kg *p.o*;. (iv) Olz+H100: receive olanzapine 2 mg/kg *b.i.d, i.p*+Hesperidin 100 mg/kg *p.o;* (v) Olz+H200: receive olanzapine 2 mg/kg *b.i.d, i.p.*+Hesperidin 200 mg/kg *p.o.*

Body weight and BMI

The body weight (g) was monitored daily throughout the study period. Body Mass Index (BMI) of each animal was calculated using formula explained by[19]

$$\text{BMI} = \frac{\text{Body weight(g)}}{\text{Nasoanal length of animal (cm2)}}$$

Food and water intake

During the study, the food intake and water intake of the animals were monitored every day. The amount of food (g) and water (mL) remaining was subtracted from the initial amounts to determine what amount was consumed.

Locomotor activity

Locomotor activity was performed weekly during the experimental period using actophotometer. The animals were brought into the testing hall and acclimatized for 30 to 60 min before the test. Each animal was placed into the actophotometer and the number of counts for each animal was recorded.[20]

Novel object recognition

After the 28th treatment, NOR was performed in three sessions (i) habituation, (ii) training, and (iii) test session. During the habituation phase, each animal was permitted to explore the arena for 10 min. After 24 hr, training session was conducted; the animals were allowed to explore two identical objects that were kept in the opposing quadrants of the arena for 5 min. After 4 hr, the test session was conducted; one of the objects was replaced, and the animals were permitted to explore again for about 2 min. The time taken by the animal exploring the novel object was noted.[21]

Oral glucose tolerance test

After the 28th treatment, OGTT was performed as per the method explained by Salahuddin M *et al.*, and Bagali RS *et al.*[22,23] Overnight fasted animals were orally administered glucose dissolved in distilled water (2 g/kg of b.w.). The glucose levels of the animals were measured using a glucometer (JanaushadiSeva Kendra, India) at 0, 30, 60, and 120 min, and AUC of glucose ($AUC_{0\text{-}120min}$) was calculated.

Homeostatic model assessment for insulin resistance (HOMA-IR)

The HOMA IR was calculated as per the formula explained by Chao PC *et al.*[24] *i.e.*

$$\text{HOMA} - \text{IR} = \frac{\text{Insulin (}\mu\text{IU/mL)} \times \text{Glucose (mmol/dL)}}{22.5}$$

Biochemical estimation

Following surgical anesthesia, blood from each animal was collected *via* cardiac puncture, and they were subsequently dissected in order to collect the adipose tissue. The adipose tissue collected was then washed, weighed, and kept in 10% v/v formalin for histological analysis by Haematoxylin and Eosin method (H & E). Total cholesterol, triglycerides, and HDL level were measured following the manufacturer's instructions using ERBA diagnostics kits. Further, LDL, and VLDL levels were calculated as explained by Salahuddin MD *et al.*[25] Plasma levels of leptin, adiponectin, and insulin were determined

following the manufacturer's instructions using a rat ELISA kit (KrishgenBiosystem). Oxidative biomarkers such as GSH, LPO, CAT, total thiol, and SOD were measured.[26]

Statistical analysis

All the data has been represented as mean±SD/SEM. To analyze the data, one-way/two-way ANOVA was used and it was followed by the required *post hoc* tests using GraphPad Prism Version 5. Statistically significant was determined by *p*-values ($p<0.05$, <0.01, and <0.001).

RESULTS

Effect of hesperidin on body weight, food intake, and water intake

Animals administered with Olz showed a significantly increased body weight starting from 16th day ($p<0.05$) to 28th day ($p<0.001$); whereas, Olz+H100, and Olz+H200 group resulted in significant reduction ($p<0.01$, and $p<0.001$) in body weight. The body weight of Olz+H50 did decline, however it was not statistically significant (Figure 1). Olz group resulted in a significant increase ($p<0.05$, $p<0.01$, and $p<0.001$) in cumulative food intake which declined significantly ($p<0.05$, and $p<0.01$) in Olz+H50, and Olz+H100 groups. Olz+H200 group showed a significant reduction ($p<0.05$, $p<0.01$, and $p<0.001$) in cumulative food intake (Figure 2). Further, it was observed that the water intake of the animals did not differ significantly.

Effect of hesperidin on BMI and abdominal circumference

It was observed that the BMI of the Olz group had notably increased ($p<0.05$), which was reduced significantly in Olz+H100 ($p<0.05$) and Olz+H200 ($p<0.01$) (Figure 3). Similarly, the abdominal circumference of the Olz group was found to be significantly higher ($p<0.001$), which was decreased significantly in Olz+H100, and Olz+H200 group ($p<0.001$) and Olz+H50 group ($p<0.05$) (Figure 4).

Effect of hesperidin on locomotor activity

In comparison to the normal group, there was a significant decline in the second week ($p<0.05$) and in the fourth week ($p<0.001$). The Olz+H50, Olz+H100, and Olz+H200 groups all showed a substantial increase in locomotor activity on week four ($p<0.05$, $p<0.01$, and $p<0.001$, respectively) (Figure 5).

Effect of hesperidin on Novel object recognition test

The discrimination ratio of the Olz group was found to be significantly lower ($p<0.001$) than that of the normal group. In comparison to the Olz group, a significant increase ($p<0.01$) in the Olz+H50 group, and ($p<0.001$) in the Olz+H100 and Olz+H200 groups in discrimination ratio was seen (Figure 6).

Effect of hesperidin on OGTT and total AUC of glucose

The glucose level of Olz group was found to be significantly higher ($p<0.001$) than the normal group, but this difference was considerably reduced ($p<0.001$) by the co-administration of hesperidin. A significantly higher ($p<0.01$) AUC of glucose was observed in the Olz group than it was in the normal group. AUC of glucose was significantly declined ($p<0.05$) in Olz+H50 and ($p<0.01$) in Olz+H100 and Olz+H200 group compared to Olz group (Figure 7).

Effect of hesperidin on HOMA-IR Index

It was observed that the HOMA-IR index of Olz group was increased significantly ($p<0.001$) than the normal group which was reduced significantly ($p<0.001$) with hesperidin co-administration (Figure 8).

Effect of hesperidin on fat pad mass

The Olz group showed a substantial rise in fat pad mass ($p<0.001$) than that of the normal group, which was decreased significantly in Olz+H100 ($p<0.01$) and Olz+H200 ($p<0.001$) group compared to the Olz group (Figure 9).

Effect of hesperidin on lipid profile

Substantial increase ($p<0.001$) in TC, TG, LDL, and VLDL level on Olz group was observed which was significantly decreased ($p<0.001$) in Olz+H200 group. Further, significant reduction in Olz+H50 ($p<0.01$), and Olz+H100 group ($p<0.001$) was observed in TC, TG, and LDL level compared to normal group. Additionally, Olz group showed a considerable decrease ($p<0.001$) in the HDL level which was significantly improved ($p<0.01$) in Olz+H200 group (Table 1).

Effect of hesperidin on plasma leptin, and adiponectin level

Olanzapine administration showed a notable increase ($p<0.001$) in plasma leptin which was significantly reduced ($p<0.001$) in

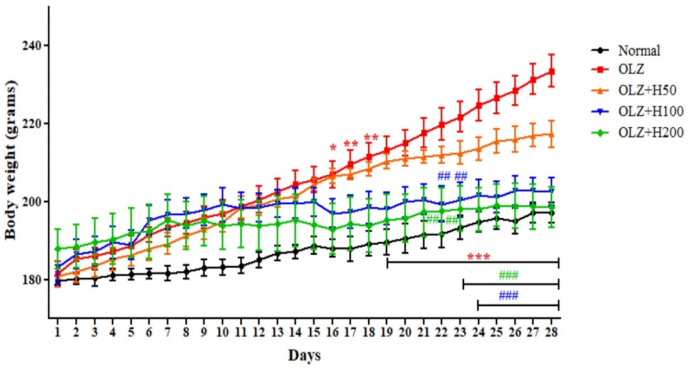

Figure 1: Effect of hesperidin on body weight.

*$p<0.05$,**$p<0.01$,***$p<0.001$ compared to normal, ##$p<0.01$, ###$p<0.001$ compared to olanzapine.

Olz+H100, and Olz+H200 compared to Olz group. Further, a significant reduction (p<0.001) in plasma adiponectin of Olz group was observed compared to normal which was improved significantly (p<0.001) in Olz+H100 and Olz+H200 group compared to Olz group (Figure 10).

Effect of hesperidin on antioxidant biomarkers

When compared to the normal group, the LPO level of the Olz group considerably increased (p<0.001), while the LPO levels of the Olz+H50, Olz+H100, and Olz+H200 groups significantly dropped (p<0.001). The total thiol in the Olz group considerably increased (p<0.01) compared to the normal group, and it significantly decreased in the Olz+H100 (p<0.01) and Olz+H200 (p<0.001) groups compared to the Olz group. Additionally, the GSH level of the Olz group notably decreased (p<0.001) when compared to the normal group, but it significantly increased in the Olz+H100 (p<0.01) and Olz+H200 (p<0.001) groups when compared to the Olz group. There were no statistical changes in the levels of CAT and SOD (Table 2).

Effect of hesperidin on histopathological analysis of adipose tissue

Adipocytes count of Olz group was significantly elevated (p<0.01) than that of the normal group which was improved in Olz+H100 and Olz+H200 group (p<0.01) compared to the normal group. Similarly, a substantial increase (p<0.01) in adipocyte size in Olz group was observed compared to that of the normal group. Further, the adipocyte size was significantly improved in Olz+H100 (p<0.05) and Olz+H200 group (p<0.01) compared to the Olz group (Figure 11).

DISCUSSION

Olanzapine, an antipsychotic medication of the second generation, is primarily used in the treatment of psychiatric conditions like schizophrenia and bipolar disorder.[4] Although the treatment of psychological disorders has been revolutionized by these drugs, they are repeatedly linked with metabolic abnormalities such as weight gain, hyperglycemia, dyslipidemia, and insulin resistance.[3,27,28] Among these conditions, the association of overweight and obesity with increased mortality, morbidity, as well as low quality of life, makes it a particular concern.[4] Despite the difficulty in managing weight gain caused by antipsychotics, lifestyle changes and drug therapy are the main approaches used to manage these side effects. However, weight gain management strategies have had limited success, which illustrates the need for further research.

To contribute to existing knowledge, we assessed the potency of hesperidin on metabolic disturbances brought on by olanzapine in female Sprague Dawley rats. Several studies have demonstrated that olanzapine administration 2 mg/kg results in hyperphagia, weight gain, dyslipidemia, hyperleptinemia, and

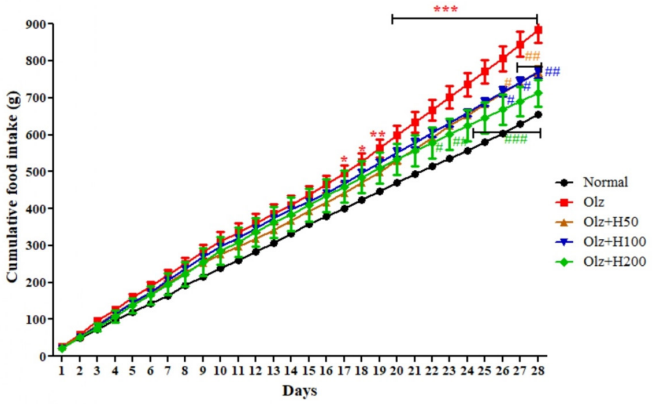

Figure 2: Effect of hesperidin on cumulative food intake.

*p<0.05,**p<0.01,***p<0.001 compared to normal, #p<0.05, ##p<0.01, ###p<0.001 compared to olanzapine.

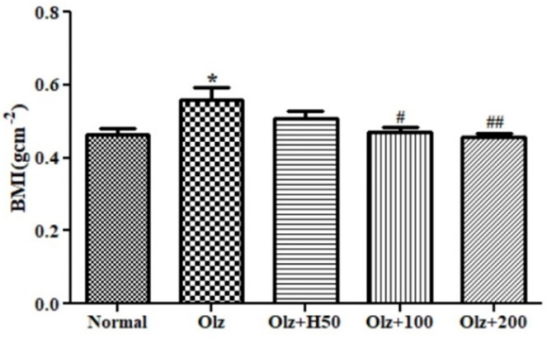

Figure 3: Effect of hesperidin on BMI.

*p<0.05 compared to normal, #p<0.05, ##p<0.01 compared to olanzapine.

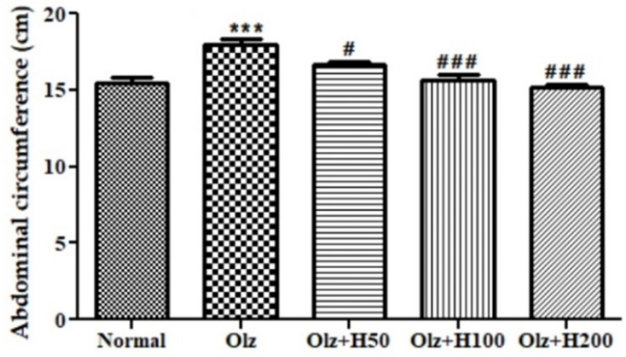

Figure 4: Effect of hesperidin on abdominal circumference.

***p<0.001 compared to normal, and #p<0.05, ###p<0.001 compared to olanzapine.

insulin resistance in female SD rats.[3,29] Similar to these studies, our research revealed that rats administered with olanzapine had substantially increased food consumption during the study period than the rats in the control group, which subsequently resulted in weight gain. However, co-administration of

hesperidin showed a significant reduction in food consumption as well as body weight, which implies that hesperidin may be able to mitigate olanzapine's detrimental effects. According to previous studies, the increased lipogenesis and impaired lipolysis caused by olanzapine contributes to fat accumulation, as well as to energy homeostasis.[9,30] Based on these reports, we utilized

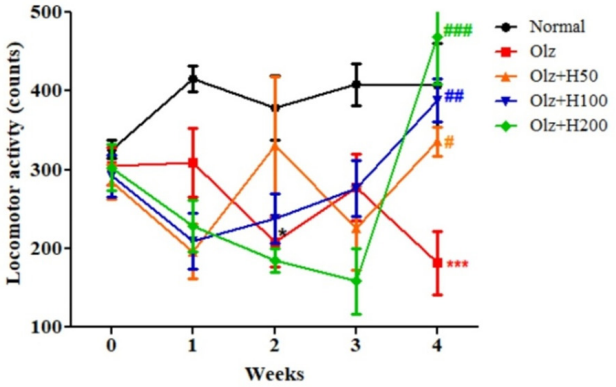

Figure 5: Effect of hesperidin on locomotor activity.

*p<0.05,***p<0.001 compared to normal, #p<0.05, ##p<0.01, ###p<0.001 compared to olanzapine.

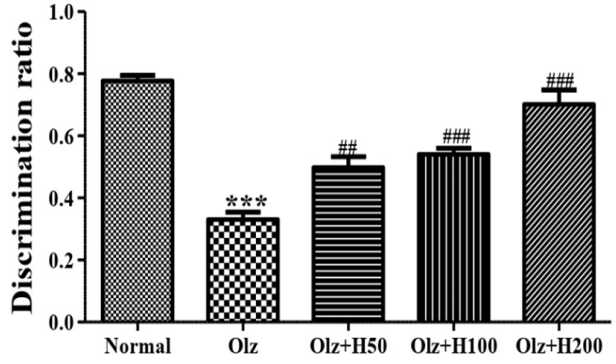

Figure 6: Effect of hesperidin on Novel object recognition test.

***p<0.001 compared to normal, and ##p<0.01, ###p<0.001 compared to olanzapine.

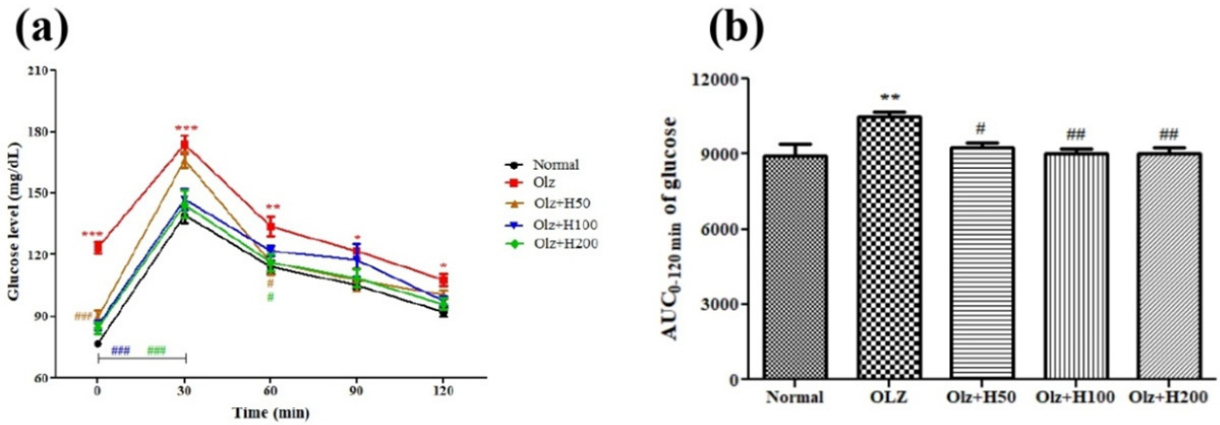

Figure 7: Effect of hesperidin on (a) OGTT and (b) AUC of OGTT.

*p<0.05, **p<0.01, ***p<0.001 compared to normal, and #p<0.05, ##p<0.01 compared to olanzapine.

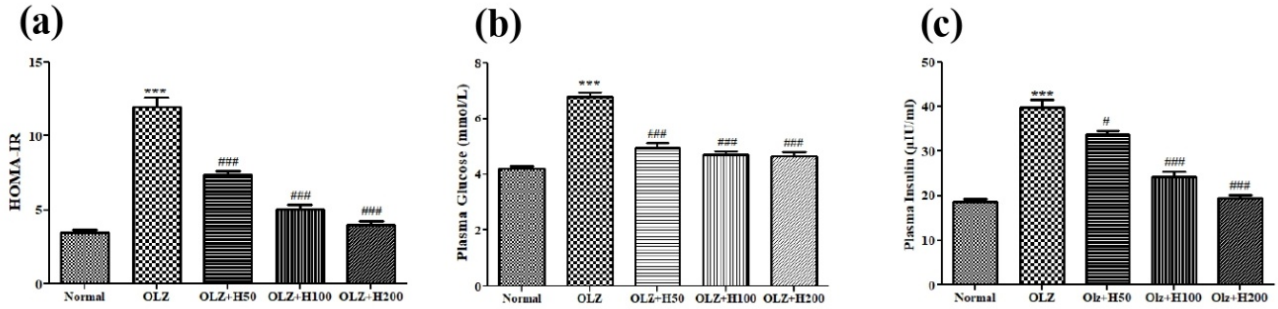

Figure 8: Effect of hesperidin on (a) HOMA-IR (b) Plasma glucose, and (c) Plasma insulin level.

***p<0.001 compared to normal, and #p<0.05 ###p<0.001 compared to olanzapine.

Table 1: Effect of hesperidin on lipid profile.

Groups	TC	TG	HDL	LDL	VLDL
Normal	108.7±3.19	76.5±5.57	22.83±0.94	70.53±3.06	15.3±1.11
Olz	142.5±3.18***	137±7.97***	15±1.23***	100.1±2.90***	27.4±1.59***
Olz+H50	122.7±4.63##	131.5±2.56##	14.17±0.83	82.2±4.09##	26.3±0.51
Olz+H100	114.8±2.98###	115±3.49###	15.83±1.13	76±2.92###	23±0.69#
Olz+H200	103.7±1.25###	90.83±4.02###	20.67±1.17##	64.83±1.01###	18.17±0.80###

Values are expressed in Mean±SEM; ***p<0.001 compared to normal, and #p<0.05, ##p<0.01, ###p<0.001 compared to olanzapine.

Table 2: Effect of hesperidin on antioxidant biomarkers.

Groups	LPO(Nano Moles/mg of protein)	GSH(µMol/mg protein)	Total thiol(µMol/mg protein)	CAT(Unit per min/mg of Protein)	SOD (Units/mL)
Normal	18.31±2.20	24.13±1.34	4.19±0.99	9.191±2.75	10.03±0.91
Olz	109.5±1.91***	8.041±0.78***	18.57±3.43**	4.208±0.50	10.12±0.15
Olz+H50	37.55±3.90###	9.639±.49	13.21±3.04	7.176±0.54	9.984±0.15
Olz+H100	34.57±1.03###	15.13±1.37##	5.493±2.77##	6.504±1.70	9.894±0.95
Olz+H200	27.42±1.97###	15.81±0.77###	1.724±0.35###	5.291±1.34	10.09±0.15

Values are expressed in Mean±SEM; **p<0.01, ***p<0.001 compared to normal, and##p<0.01, ###p<0.001 compared to olanzapine.

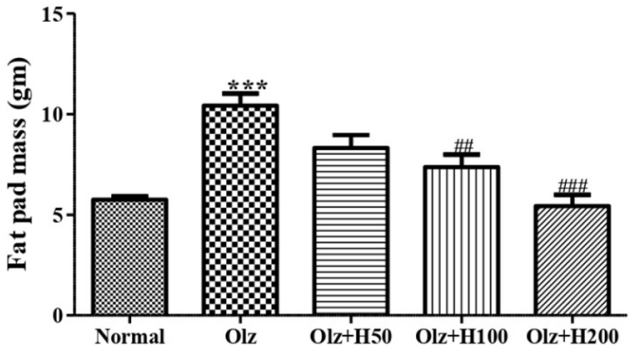

Figure 9: Effect of hesperidin on fat pad mass.

***p<0.001 compared to normal, and ##p<0.01, ###p<0.001 compared to olanzapine.

actophotometer to assess energy expenditure, and found notable reduction in the locomotor activity of the olanzapine-treated rats which was enhanced significantly by the co-administration of hesperidin. Additionally, the olanzapine group had significantly higher BMI and abdominal circumference, both of which were reduced with the co-administration of hesperidin. Compared to olanzapine group, hesperidin co-administration in this study resulted in a significantly decreased total fat mass.

Several studies have demonstrated that olanzapine treatment causes hyperglycemia and disruption of glucose metabolism which leads to insulin resistance. Long-term use of olanzapine has been linked to insulin resistance as it dramatically increased plasma levels of pro-inflammatory cytokines.[27,28] In contrast, hesperidin has been shown to have an anti-hyperglycemic effect and improved insulin resistance in animal models of high-fat diets.[31-33] Thus, we performed OGTT, where the olanzapine group resulted in significantly higher blood glucose levels compared to the normal group, but hesperidin treatment effectively prevented these effects. The HOMA-IR model was employed in this study to evaluate insulin resistance, and it was observed that co-administration of hesperidin with olanzapine decreased the HOMA-IR index, indicating that hesperidin treatment reduced the insulin resistance brought on by olanzapine.

Leptin and adiponectin, are the major hormones secreted by adipocytes, that have an integral role in the development of obesity and insulin resistance.[34,35] Regarding the association between antipsychotics and leptin levels, multiple studies have presented contradictory results. According to some research, low levels of leptin hinder the ability of the hypothalamus to receive signals of satiety, which increases appetite and causes weight gain.[10] While other studies, found elevated leptin levels, suggesting that

high levels of leptin are a consequence of weight gain.[36-38] Like the latter, our study demonstrated considerably higher leptin levels in the olanzapine group compared to the normal, and these differences were mitigated by co-administration of hesperidin. Researchers suggest that leptin may not be the cause of weight gain in antipsychotic-induced models of obesity, but rather, a rise in leptin may be caused by the increased adiposity; resulting in hypothalamic leptin resistance which worsens obesity by decreasing anorexigenic and energy expenditure signals.[39-41] In our investigation, it was corroborated by enlarged adipocytes which were observed in the histological analysis. The histological examination showed that whereas olanzapine resulted in the hyperplasia and hypertrophy of adipocytes; co-administration of hesperidin with olanzapine decreased the size and number of

adipocytes. Moreover, leptin is also reported to exhibit a direct correlation with BMI, body weight percentage, hyperinsulinemia as well as HOMA-IR.[42] In this study, we analyzed each of these parameters, and we observed that co-administration of hesperidin showed a positive effect by decreasing the body weight and BMI as well as improving the HOMA-IR index, indicating that hesperidin may have the potential efficacy to reduce the negative effects brought on by olanzapine.

Adiponectin is known as the anti-inflammatory cytokine, it promotes insulin signalling as well as lipid metabolism to maintain the lipid profile. Decreased level of adiponectin leads to chronic inflammation in adipose tissue which subsequently

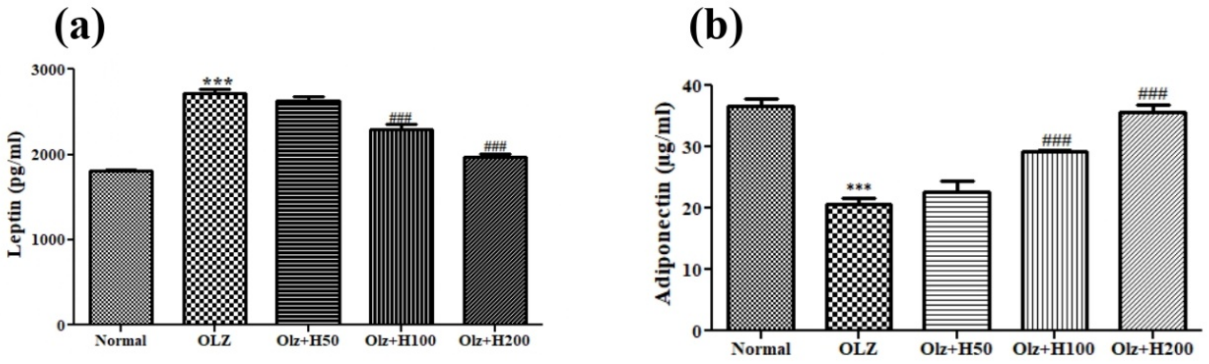

Figure 10: Effect of hesperidin on (a) plasma leptin, and (b) plasma adiponectin level.

****p*<0.001 compared to normal, and ###*p*<0.001 compared to Olanzapine.

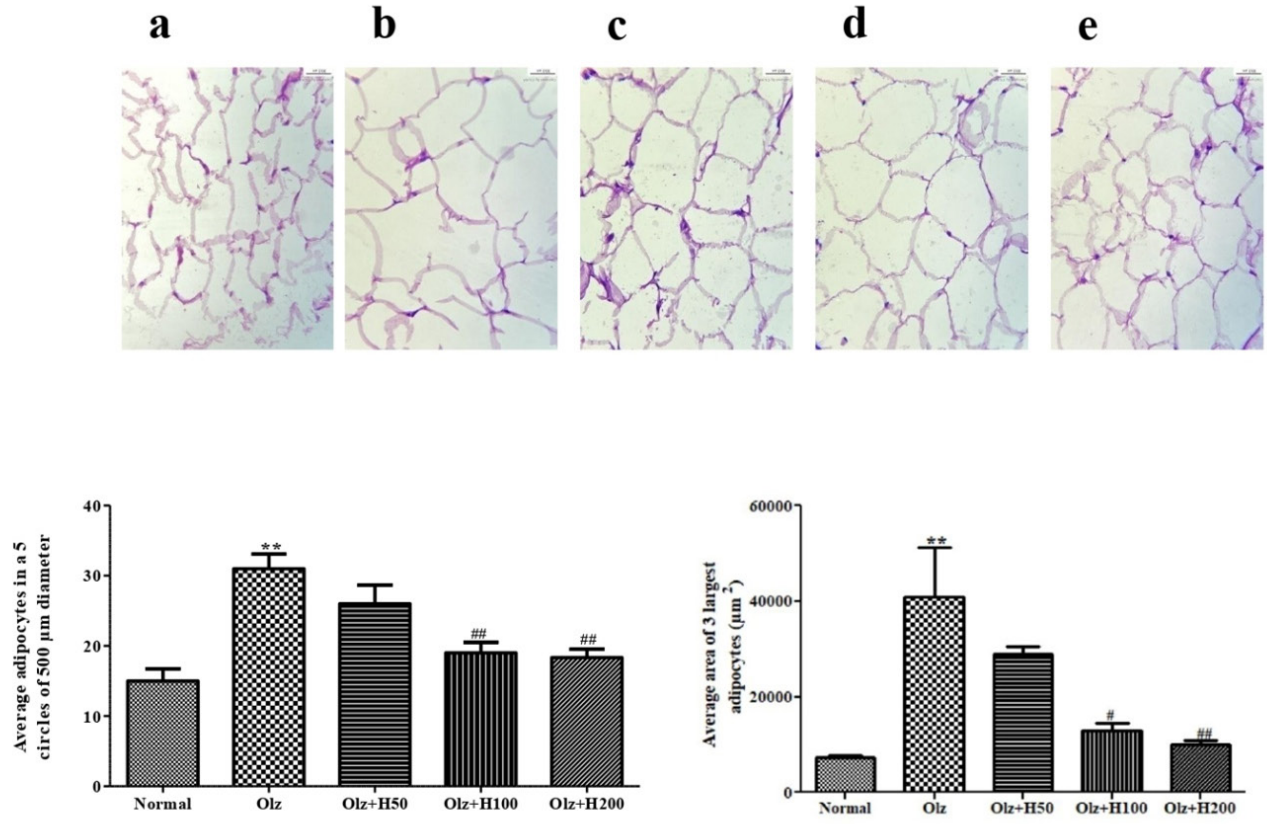

Figure 11: Histopathological analysis of adipose tissue magnification HE at 40X (a) Normal, (b) Olanzapine, (c) Olz+H50, (d) Olz+H100, and (e) Olz+H200.

***p*<0.01 compared to normal, and #*p*<0.05, ##*p*<0.01 compared to olanzapine.

promotes the development of insulin resistance.[43,44] Plasma adiponectin is also negatively correlated with BMI, abdominal circumference and oxidative stress.[45] In consistent with these studies, our study showed a significantly decreased plasma adiponectin level in the olanzapine group, which was improved with hesperidin administration. Improvement in adiponectin level could contribute to the improvement of insulin resistance and lipid profile in this study.

Often, insulin resistance and dyslipidemia are associated and reinforce one another, raising the risk of cardiovascular and metabolic disease. It has been suggested that IR results in alterations in lipid and lipoprotein metabolism that lead to dyslipidemia.[46] Hence, we measured the lipid levels including total cholesterol, total triglyceride, HDL, LDL, and VLDL, and found that olanzapine altered the lipid levels significantly. However, co-administration of hesperidin with olanzapine improved the lipid profiles, indicating its potential to mitigate olanzapine-induced dyslipidemia. These outcomes were in line with earlier research that showed hesperidin to have anti-adipogenic properties in both *in vitro* and *in vivo* experiments *via* upregulation of pAMPK expression and downregulation of SREBP-1C, ACC, and FAS expression.[47,48]

Insulin resistance, fat deposition, and oxidative stress have all been linked; overexpression of oxidative stress damages cellular structures and prevents the generation of antioxidant mechanisms, which leads to the emergence of complications associated with obesity.[41] Consequently we measured markers of oxidative stress and antioxidant defence systems such as lipid peroxidation, glutathione, catalase, superoxide dismutase, and total thiol in this study. Consistent with previous studies, olanzapine disrupted the antioxidant levels in the rats, but co-administration of hesperidin significantly improved the levels of these oxidative stress markers.[49-51]

According to some research, olanzapine may have detrimental impacts on cognition,[52-54] while others report improvement of the cognitive function.[55,56] The effect of olanzapine may differ depending on the particular cognitive domain being studied, dosage, and the duration of the therapy.[54,57] In this study, olanzapine administration led to impaired recognition memory and learning, which is assessed by the failure to distinguish between familiar and novel objects in the NOR test. This behavioral deficiency was significantly improved in the hesperidin treated group. This result complies with the previous studies where hesperidin has been reported to be able to improve cognitive function in rodents by inducing synapse formation and enhancing hippocampal neurogenesis processes.[58,59]

CONCLUSION

The present study demonstrates that hesperidin has the potential to mitigate metabolic disturbances brought on by olanzapine in female Sprague Dawley rats. Co-administration of hesperidin not only improved metabolic parameters but additionally exhibited a beneficial effect on memory performance. This shows that hesperidin may be used as an adjuvant therapy alongside olanzapine, without compromising olanzapine's primary therapeutic effects. However, further preclinical and clinical research is required to validate these encouraging findings and translate these findings into safe and efficient therapeutic approaches for those on olanzapine therapy.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

AUTHOR CONTRIBUTIONS

D.T. performed the experiment, analysis and interpretation of data, and drafting of the manuscript, S.S.J. contributed in supervision of the study, editing and revision of the manuscript, B.M.P. contributed in conceptualization, design of the study and revision of the manuscript. B.K. contributed in revision of the manuscript.

ABBREVIATIONS

AUC: Area Under Curve; **BMI:** Body Mass Index; **CAT:** Catalase; **GSH:** Glutathione; **HDL:** High Density lipoprotein; **HOMA-IR:** Homeostatic Model Assessment for Insulin Resistance; **IAEC:** Institutional Animal Ethical Committee; **LDL:** Low density lipoprotein; **LPO:** Lipid peroxidation; **NOR:** Novel object recognition test; **OGTT:** Oral glucose tolerance test; **SD:** Sprague Dawley; **SOD:** Superoxide dismutase; **TC:** Total Cholesterol; **TG:** Triglyceride; **VLDL:** Very low density lipoprotein.

ANIMALS AND ETHICAL CLEARANCE

The IAEC of KLE College of Pharmacy, Belagavi granted ethical clearance for the animal investigations bearing resolution no. (KLECOP/CPCSEA-Reg.No.221/Po/Re/S/2000/CPCSEA,resolution no.30).

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