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Original Article

Effect of *Caralluma fimbriata* Hydroalcoholic Extraction on Olanzapine-Induced Hyperphagia and Metabolic Changes in Rats

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ABSTRACT

Background: Olanzapine an atypical antipsychotic, is known to cause metabolic side effects such as weight gain, hyperlipidemia and oxidative stress, contributing to the development of metabolic syndrome. *Caralluma fimbriata* a traditional plant has shown potential in regulating weight and improving lipid metabolism. This study aims to evaluate the effects of *Caralluma fimbriata* hydro-alcoholic extract (CFE) on metabolic changes induced by olanzapine in rats. **Materials and Methods:** Thirty female Sprague-Dawley rats (180-190g) the rats were maintained under controlled environmental conditions (22±2ºC, 12 hr light/dark cycle) with free access to standard diet and water. Following a one-week acclimatization period, they were randomly divided into five experimental groups Normal (vehicle), Olanzapine (OLZ 2 mg/kg/day), OLZ+*Caralluma fimbriata* 100 mg/kg (CFE100+OLZ), OLZ+CFE 200 mg/kg (CFE200+OLZ), and OLZ + CFE 400 mg/kg (CFE400+OLZ). Treatments were administered orally for 21 days. Daily body weight and food intake were recorded. Blood was collected for lipid profile analysis. Upon sacrifice, organ weights and oxidative stress markers were assessed. **Results:** Co-administration of CFE with Olanzapine (OLZ) resulted in a significant reduction in OLZ-induced weight gain and hyperphagia. CFE also demonstrated positive effects on the metabolic changes, improving body weight gain compared to OLZ-only treated rats. Furthermore, CFE notably improved the lipid profile, demonstrating significant antihyperlipidemic effects. **Conclusion:** The hydro-alcoholic extract of *Caralluma fimbriata* effectively mitigates olanzapine-induced weight gain, oxidative stress and disturbances in lipid metabolism indicating its potential as an adjunctive therapy for managing olanzapine-induced metabolic side effects.

Keywords: Olanzapine, Lipid Metabolism, Weight Gain, *Caralluma fimbriata*.

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INTRODUCTION

Olanzapine, a second-generation anti-psychotic that was approved by the FDA in 1996 for the treatment of schizophrenia has been available in generic form since 2011. Additionally it is utilized as a long-acting injectable for schizophrenia and in conjunction with fluoxetine to treat treatment-resistant depression and bipolar depression (Thomas *et al*., 2023, Leucht *et al*., 2009, Meftah A *et al*., 2020). Olanzapine, however, has serious side effects, especially weight gain (Svensson *et al*., 2029, Lin *et al*., 2018) and a higher risk of metabolic syndrome which includes diabetes, insulin resistance and dyslipidemia (Hardy *et al*., 2011, Lanktree *et al*., 2018). Several strategies have been investigated to treat olanzapine-induced weight gain, including mixing olanzapine with betahistine, metformin and curcumin, *zingiber officinale* (Deng *et al*., 2012, Parasuraman *et al*., 2017, Ullagaddi *et al*., 2021). Despite these attempts weight gain remains a polygenic condition involving several proteins that contribute to metabolic syndrome and obesity. There is still a need for therapeutic approaches that can reduce these adverse effects without compromising olanzapine's therapeutic benefits. *Caralluma fimbriata* a succulent plant native to India, North Africa and the Middle East, is traditionally used for its appetite-suppressing properties. It has been valued for enhancing endurance and reducing hunger during scarcity. Modern research supports its role in weight management by modulating hunger-regulating neurotransmitters and metabolic pathways. Phytoconstituents like pregnane glycosides, flavonoids and saponins contribute to its effects. Clinical studies suggest it may reduce food intake and body weight but caution is advised for pregnant, breastfeeding women and those with pre-existing health conditions. Ongoing

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research explores its therapeutic potential (Kamalakkannan *et al.*, 2010, Gujjala *et al.*, 2017, Sudhakara *et al.*, 2014).

The effects of a *Caralluma fimbriata* extract of on weight growth, food intake, lipid profile, oxidative stress markers and organ weight will be examined in a model of olanzapine-induced weight gain using female Sprague-Dawley rats.

MATERIALS AND METHODS

Animals

National Lacsmi biofarm, Pune, provided healthy female Sprague-Dawley rats weighing 180±10 g the rats were given a regular pellet meal and unlimited water while living in suboptimal settings (22-25°C, 65-70% humidity, and a 12:12 light/dark cycle). Pravara Rural College of Pharmacy's IAEC accepted the study protocol (CPCSEA Reg. No: 1942/PO/Re/S/17/CPCSEA/2023/01/05/01). Prior to the trial, the animals were acclimated to a 12:12 light/dark cycle for seven days.

Chemicals

Olanzapine was bought in Mumbai, India, from Yarrow Chem Products. 0.1 N hydrochloride acid was used to dissolve olanzapine, 0.1 N NaOH was used to bring the pH down to 5.5 adjust the final volume by using distilled water (Parasuraman *et al.*, 2017).

Preparation of hydroalcholic extract of *Caralluma fimbriata*

The extract of *Caralluma fimbriata* was sourced from Green-Chem Herbal Extracts, Bangalore, India. The aerial parts of the plant were collected, shade-dried, and ground. 100 g of the plant material were extracted using 40% aqueous alcohol. The extract was dissolved in distilled water before use (Sudhakara *et al.*, 2014).

Total Phenol Content

The total phenolic content of *Caralluma fimbriata* extracts was measured using the Folin-Ciocalteu method (Senguttuvan *et al.*, 2014).

Total Flavonoid Content

The total flavonoid content of *Caralluma fimbriata* extracts was determined using the Dowd method (Dixit *et al.*, 2022).

Study Design

Female SD rats were chosen as the animals, and they were divided into five groups of six using random numbers. The medications were given twice a day for 21 days.

1) **NORMAL:** Receives Vehicle (0.1 N HCL adjusted pH with 0.1 N NaOH) 2 mL/kg divided in two dose at 12 hr interval,
2) **OLZ:** Receives olanzapine injected by 2 mg/kg/day, divided in 2 dose at 12 hr interval i.p administration for 21 days Served as control (Kanagali *et al.*, 2022),
3) **CFE100+OLZ:** Receives olanzapine injected by 2 mg/kg/day, i.p. divided in 2 dose. at 12 hr interval+TCE extract 100 mg/kg one dose orally administration for 21 days,
4) **CFE 200+OLZ:** Receives olanzapine injected by 2 mg/kg/day, i.p. divided in 2 dose at 12 hr interval+TCE extract 200 mg/kg one dose orally administration for 21 days,
5) **CFE 400+OLZ:** Receives olanzapine injected by 2 mg/kg/day, i.p. divided in 2 dose at 12 hr interval+CFE extract 400 mg/kg one dose orally administration for 21 days. The animals in each of the five groups' three cages held two each, and they were all fed the same pellet diet.

Measurement of body weight and food intake

Food consumption was monitored daily during the trial. Were measured every day for 24 hr. The following formula was used to determine the food intake for that day in separated metabolic cage place one animal and put feed pellete 5 g after 24 hr remaining food weighed and below formula use for calculation (Ullagaddi *et al.*, 2021).

$$\text{Food intake} = \frac{\text{amount of food added}}{\text{remaining amount of food}}$$

Measuring % gain body weight

Body weight and food intake were recorded from the first to the twenty-first day. The percentage rise in body weight for the relevant day was calculated using the following formula (Ullagaddi *et al.*, 2021).

$$\%\ \text{gain in body weight} = \frac{\text{Final Weight} - \text{Initial Weight}}{\text{Initial weight}} \times 1000$$

Biochemical analysis

Blood was drawn into Eppendorf tubes using the retro-orbital method at the conclusion of the experiment. Samples for following coagulation were centrifuged at 4000 rpm for 5 min at 4°C. For the purpose of biochemical analysis, the serum was isolated and kept at -20°C. A glucometer (Accu-Chek Instant, India) was used to measure the levels of glucose. Kits from Trans asia Biomedicals Ltd., AUTOSPAN, and PBHDL these assays were employed to determine Triglycerides (TG), Total Cholesterol (TC), and High-Density Lipoprotein (HDL). Levels of Low-Density Lipoprotein (LDL) and Very-Low-Density Lipoprotein (VLDL) were subsequently calculated were calculated using standard formula (Ullagaddi *et al.*, 2021).

$$\text{VLDL (mg/dL)} = \frac{TG}{5}\text{LDL (mg/dL)} = \text{TC- (HDL+VLDL)}$$

Tissue collection

Weigh an animal's organ. Quickly remove the necessary organ and wash the ice-cold tris buffer twice. Accurately weigh the tissue, then prepare 10% w/v of it with ice-cold tris buffer (10 mM, pH 7.4). Slice the tissue into small pieces, use a homogenizer to create a clear homogeneous mixture, and then place the tissue in a plastic centrifuge set on high speed cooling (6000 rpm for 20 min). Maintain the homogenate in a frozen state.

In liver tissue measuring the amount of Malondialdehyde (MDA)

Malondialdehyde (MDA) levels in liver tissue were measured using the Thiobarbituric Acid (TBA) reaction. 200 mg of liver samples were homogenized in 1.15% KCl to create a 10% tissue homogenate. 500 µL of this homogenate were mixed with 3 mL of 1% phosphoric acid and 1 mL of 0.6% TBA. The combination was heated for 45 min in boiling water, then cooled and vortexes with 4 mL of butanol. After 15 to 20 min of centrifugation the top pink layer was seen at 532 nm. The MDA content of the tissue was expressed as nmol/g (Kumar *et al*., 2012).

In liver tissue measuring the amount of Glutathione (GSH)

The assay is based on the interaction of sulfhydryl groups with 5, 5'-dithiobis-(2-nitrobenzoic acid) (DTNB), producing a yellow-colored compound that exhibits maximum absorbance at 412 nm. For the procedure, 200 mg of liver tissue was homogenized in phosphate buffer (pH 7.4) to obtain a 10% homogenate. A 500 µL aliquot of this homogenate was mixed with 500 µL of 10% Trichloroacetic Acid (TCA) and centrifuged at 10,000 rpm for 6 min. Subsequently, 500 µL of the resulting supernatant was added to 2.5 mL of phosphate buffer (pH 8) and 500 µL of DTNB solution. Absorbance was recorded at 412 nm, and reduced Glutathione (GSH) concentration was determined from a standard calibration curve (Mihara *et al*., 1978).

In liver tissue measuring the amount of Catalase (CAT) in liver tissue

Catalase activity was assessed by mixing 50 µL of tissue supernatant with 1.0 mL of 50 mm phosphate buffer (pH 7) and 0.1 mL of 30 mm hydrogen peroxide. The change in absorbance was monitored at 240 nm for 30 sec at 5 sec intervals, and the rate of decrease was used to calculate enzyme activity. Results were expressed as units (U) per gram of tissue (Ellman *et al*., 1959).

Measuring the amount of Superoxide Dismutase (SOD) in liver tissue

640 µL of distilled water, 10 µL of 0.3% Triton X-100, 100 µL of 1 mm EDTA, 100 µL of 240 µm NBT, 25 µL of tissue supernatant, and 1 mm hydroxylamine were mixed to create a mixture for the enzyme activity test. To track the increase in the reaction's slope, spectrophotometric measurements were taken in kinetic mode for 3 min at a wavelength of 560 nm at 1 min intervals. The enzyme activity was measured in units (U) per gram of tissue (Aebi *et al*., 1984).

Histopathological Studies

Liver tissues removal was done from euthanized animals and immediately fixed using 10% neutral buffered formalin (pH 7.4±0.2) at room temperature (25±2°C) for 48 hr (Mark *et al*., 2007, Zeng *et al*., 2023).

Statistical analysis

All of the data are analyzed using GraphPad Prism version 10, the results are displayed as Mean±SEM. Body weight, food and water intake, blood glucose levels during the OGTT, and locomotor activity were all investigated using two-way ANOVA and Tukey's *post hoc* test. Mean±SEM is used to show oxidative stress in addition to the lipid profile. One-way ANOVA using GraphPad Prism software (version 10) and Bonferroni *post hoc* tests.

RESULTS

Effect on body weight

Olanzapine-treated rats showed significant weight gain ($p<0.0001$) vs. Normal rats. Co- administration of CFE (100, 200, 400 mg/kg) with Olanzapine significantly reduced weight gain ($p<0.001$) from day 6 to 21 (Table 1).

Effect on cumulative food intake

Co-administration of CFE (200, 400 mg/kg) with Olanzapine (2 mg/kg) significantly decreased cumulative food intake ($p<0.0001$) from day 6 to 21. Olanzapine-treated rats showed increased cumulative food intake ($p<0.0001$) compared to Normal rats on day 21 (Table 2).

Effect of CFE on lipid profile

Significant alterations were detected in the lipid profile parameters-Triglycerides (TG), Total Cholesterol (TC), High-Density Lipoprotein (HDL), Low-Density Lipoprotein (LDL), and Very-Low-Density Lipoprotein (VLDL)-among the study groups ($p<0.0001$). Administration of olanzapine resulted in marked increases in TG, TC, LDL, and VLDL levels (all $p<0.0001$), accompanied by a significant reduction in HDL concentration ($p<0.0001$). Co-treatment with *Caralluma fimbriata* extract (CFE) at 200 and 400 mg/kg effectively mitigated olanzapine-induced dyslipidemia, as shown by elevated HDL levels ($p<0.01$) and reduced TG ($p<0.001$) and VLDL ($p<0.001$) values. In addition, supplementation with CFE at 100, 200, and 400 mg/kg produced a significant decline in LDL ($p<0.0001$) and TC ($p<0.001$) compared with olanzapine alone (Table 3).

Table 1: Body weight gain (%) at different interval (Days) in rat treated with vehicle olanzapine (2 mg/kg) Olanzapine+CFE (100, 200, 400 mg/kg/day).

Group/Days	Mean±SEM						
	Days 3	6	9	12	15	18	21
Normal	0.097±0.097	1.262±0.098	2.628±0.201	4.077±0.265	5.567±0.337	6.723±0.333	8.183±0.348
Olanzapine	1.065±0.182	3.372±0.308	6.847±0.273	9.942±0.322 ****	14.315±0.785 ****	16.98±0.414 ****	19.495±0.214 ****
CFE100+ OLZ	1.754±0.501	3.703±1.414	8.284±1.183	8.382±1.398	10.623±1.371 #	132.1±1.967 #	12.9±2.650 ####
CFE200+ OLZ	1.744±0.397	2.186±0.616	2.519±0.715 ##	3.294±1.160 ####	5.038±0.789 ####	4.554±0.726 ####	7.267±0.469 ####
CFE400+ OLZ	0.821±0.240	1.259±0.461	1.065±0.277 ##	1.550±0.746 ####	1.550±0.649 ####	1.258±0.460 ####	1.555±0.653 ####

All the data are represented in Mean±SEM **** p<0.0001 compared to normal # p<0.05, ## p<p<0.01, #### p<0.0001 compared to olanzapine.

Table 2: Cumulative Feed intake at Different Interval (Days) rat treated with vehicle olanzapine (2mg/kg) Olanzapine+CFE (100, 200, 400 mg/kg/day).

Group/ Days	Mean±SEM						
	3	6	9	12	15	18	21
Normal	64.633 ±2.331	119.910 ±5.535	170.437 ±6.789	230.17 ±5.916	286.407 ±8.353	353.623 ±7.576	407.487 ±11.508
Olanzapine	48.887 ±1.226	104.717 ±3.515	172.267±3.564	241.37 ±3.010	301.013 ±2.764	371.073 ±3.378	444.357 ±3.588 ****
CFE100+ OLZ	51.167 ±1.216	107.667 ±2.348	162.883±2.348	216.833 ±2710 #	265.000 ±2.834 ###	309.000 ±3.286 ####	361.500 ±4.427 ####
CFE200+ OLZ	29.487 ±0.423	56.653 ±1.979 ####	85.930±3.298 ####	115.917 ±2.682 ####	148.223 ±3.222 ####	181.517 ±3.881 ####	214.597 ±4.421 ####
CFE400+ OLZ	28.500 ±2.288	56.667 ±4.228 ####	84.500±7.526 ####	114.667 ±10.016 ####	150.330 ±10.016 ####	188.350 ±9.923 ####	220.433 ±12.835 ####

All the data are represented in Mean±SEM **** p<0.0001 compared to normal # p<0.05, ## # p<0.001, #### p<0.0001 compared to olanzapine.

Table 3: Lipid profile in rats treated with vehicle olanzapine (2 mg/kg/day), olanzapine plus CFE (100,200,400 mg/kg/day).

Groups	TC (mg/dL)	TG (mg/dL)	HDL (mg/dL)	LDL (mg/dL)	VLDL (mg/dL)
Normal	46.21±1.500	40.58±1.827	41.78±0.5613	8.117±0.3648	8.117±0.3648
Olanzapine	62.61±0.9840 ****	88.19±3.432 **	25.32±1.126 ****	17.64±0.6866 *	17.64±0.6866 *
CFE100+OLZ	63.27±0.9855	108.7±13.62	22.36±2.236	20.01±3.843	21.74±2.724
CFE200+OLZ	46.42±1.288 ####	53.21±5.873 #	22.28±2.254	13.50±2.268	7.773±3.457 #
CFE400+OLZ	30.57±1.078 ####	52.33±1.144 #	27.88±2.012	-7.775±1.495	10.47±0.2297 ####

All data are represented in Mean±SEM (n=6), * p<0.05, **p<0.01, **** p<0.0001 compared to normal, # p<0.05, #### p<0.0001 compared olanzapine.

Effect on organ weight

A notable variation in the weight of the organs was noted. When CFE (100,200,400 mg/kg) and olanzapine were administered together, there was a substantial decrease in the weight of the liver (p<0.0001), heart (p<0.05) and adipose tissue when compared to rats treated with olanzapine. However, as compared to the olanzapine group, there was no discernible difference in kidney weight. Compared to the typical and non-significant difference in heart and kidney weight, the olanzapine-treated group had significantly greater liver and adipose tissue organ weight (Table 4).

Effect of on MDA, GSH, CAT and SOD levels of liver tissue

Catalase (CAT) Olanzapine treatment showed non-significant changes in liver CAT levels compared to Normal group. Co-administration of CFE (100-400 mg/kg) with olanzapine also showed non-significant changes in CAT levels. Malondialdehyde (MDA) Olanzapine treatment significantly increased MDA levels in liver tissue (p<0.05) compared to Normal group. Co-administration of CFE (100-400 mg/kg) with olanzapine significantly decreased MDA levels (p<0.01). Superoxide Dismutase (SOD) Olanzapine treatment significantly decreased SOD levels in liver tissue compared to Normal group. Co-administration of CFE (100-400 mg/kg) with olanzapine significantly increased SOD levels (Table 5).

Effect of Olanzapine and co- administration of CFE (100, 200, 300 mg/kg) plus OLZ (2 mg/kg) on Liver Histopathology alterations in female SD rat

Hematoxylin and eosin-stained sections of liver tissues collected. H and E staining was used to determine various changes viz. Abnormalities of liver cells and Necrosis of hepatic cells (Magnification: 10X and 40X). Microscopic examination of liver sample from Normal group did not show any abnormality of pathologic al significance. Assessment of liver sample from OLZ group showed Hepatic cell with ballooning degeneration, focal necrotic cell death and diffuse changes. Abnormality was detected in liver tissues. CFE100, CFE200, CFE400 with OLZ groups show Normal hepatocytes arranged, with obvious sinusoids, and central vein no abnormality detected. The severity and incidence rate of these changes was reduced after treatment with CFE 100, CFE200, CFE 400 Plus OLZ (Figure 1).

DISCUSSION

The present study aimed to investigate the potential therapeutic effects of *Caralluma fimbriata* extract (CFE) in mitigating the metabolic and biochemical alterations induced by olanzapine, a commonly prescribed atypical antipsychotic. Olanzapine, while effective for treating psychiatric disorders, is known to induce a range of metabolic side effects including weight gain, dyslipidemia, and increased oxidative stress. The results of the present study provide promising evidence that CFE may serve as an adjunctive therapy to counteract these adverse effects.

The administration of olanzapine (2 mg/kg/day) for 21 days resulted in a significant increase in body weight, which is consistent with previous reports of olanzapine-induced hyperphagia and weight gain in animal models (Gujjala *et al.*, 2016, Ferno *et al.*, 2011). In the current study, CFE administration (100, 200, and 400 mg/kg) significantly reduced body weight gain in olanzapine-treated rats. Notably the highest dose (400 mg/kg) exhibited the most pronounced effect which aligns with findings from prior studies showing CFE's potential as an appetite-suppressant and anti-obesity agent (Sudhakara *et al.*, 2014). The dose-dependent reduction in food intake observed in the CFE-treated rats suggests that CFE may help regulate appetite and improve metabolic balance, likely through its bioactive compounds.

Olanzapine administration led to significant alterations in lipid metabolism, including increased Triglycerides (TG), Low-Density Lipoprotein (LDL), Very-Low-Density Lipoprotein (VLDL) and Total Cholesterol (TC) alongside a reduction in High-Density Lipoprotein (HDL). These dyslipidemia effects have been widely documented in literature as part of the metabolic syndrome associated with olanzapine use (Gujjala *et al.*, 2016, Ferno *et al.*,

Table 4: Organ weight rats treated with vehicle olanzapine (2 mg/kg/day), OLZ plus TCE (100, 200, 400 mg/kg/day). Plus CFE (100, 200, 400 mg/kg/day).

GROUPS	Heart(gm.)	Adipose tissue (gm)	Kidney (gm)	Liver (gm)
NORMAL	0.61±0.03	5.03±0.22	0.64±0.01	6.31±0.25
OLZ	0.67±0.03	8.14±0.38 ****	0.76±0.05	7.44±0.12 **
CFE100+OLZ	0.58±0.01	5.15±0.26 ####	0.68±0.02	6.60±0.25
CFE200+OLZ	0.59±0.02	4.23±0.18 ####	0.63±0.00	5.74±0.18 ####
CFE400+OLZ	0.52±0.02 #	3.75±0.42 ####	0.61±0.01	5.55±0.19 ####

All data are represented in Mean±SEM (n=6), **p<0.01, **** p<0.0001 compared to normal, # p<0.05, #### p<0.0001 compared to olanzapine

Table 5: Oxidative stress in rats treated with vehicle Olanzapine (2 mg/kg/day), Olanzapine+CFE (100, 200, 400 mg/kg/day).

Groups	CAT (micromole of H_2O_2/ gm of tissue)	GSH (micromole of H_2O_2/ gm of tissue)	MDA (micromole of H_2O_2/ gm of tissue)	SOD (unit/gm of tissue)
Normal	7.960±0.1436	1275±75.95	28.62±3.011	0.3283±0.07631
Olanzapine	7.717±0.0076	824.5±18.34 ***	53.54±6.402 **	0.5750±0.07513 **
CFE100+OLZ	7.723±0.0968	844.0±22.09	27.77±2.034 ##	0.7550±0.03394 ##
CFE200+OLZ	7.757±0.2780	880.5±16.85	37.94±6.140	05633±0.04821
CFE400+OLZ	7.928±0.1712	911.5±27.52	33.28±2.425	0.4733±0.1094

All data are represented in Mean±SEM (n=6), ** p<0.01, *** p<0.001 compared to normal, ## p<0.01 compared to Olanzapine.

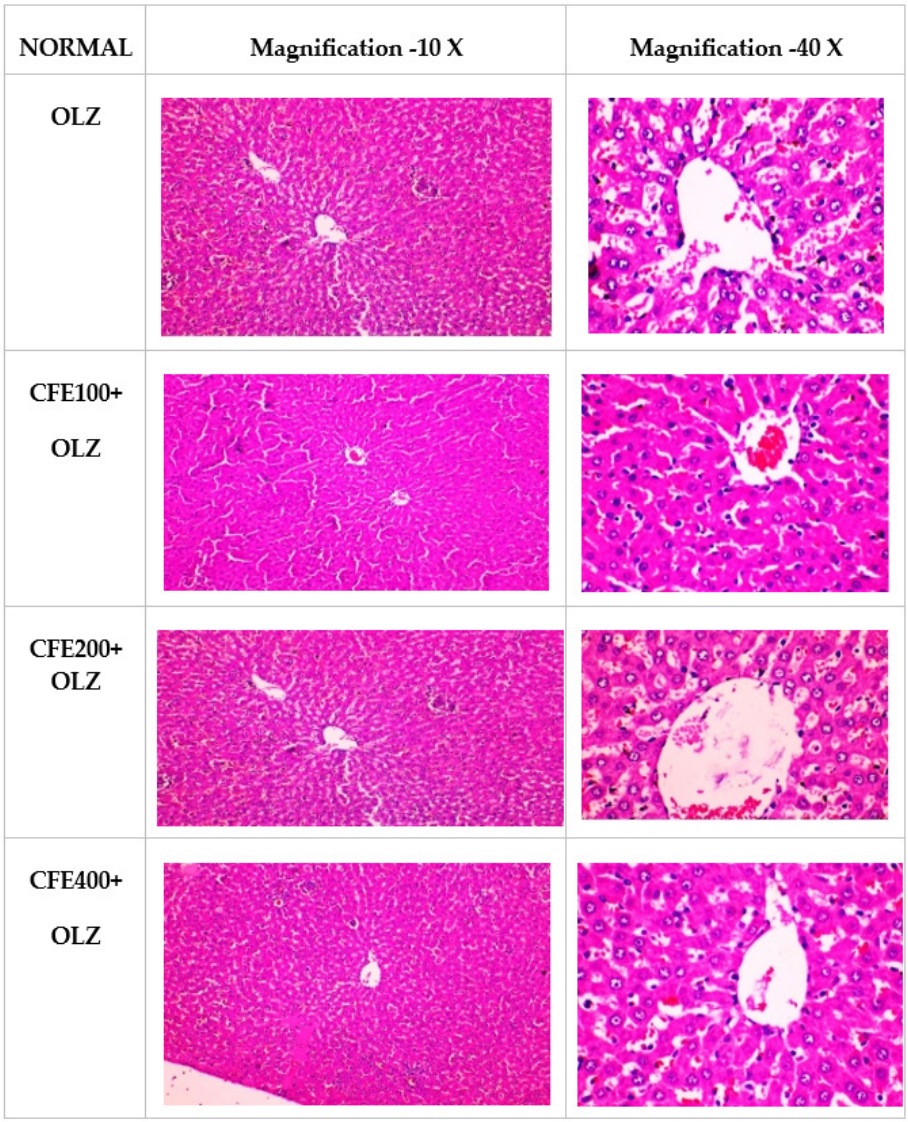

Figure 1: Effect in rats treated with vehicle olanzapine (2 mg/kg/day),OLZ plus CFE (100, 200, 400 mg/kg/day) on liver histopathological changes in SD rat. Hematoxylin and eosin-stained sections of liver tissues collected. Hand E-staining was used to determine various changes viz. Abnormalities of liver cells and Necrosis of hepatic cells (Magnification: 10X and 40X). Microscopic Examination of Liver Sample From Normal group not show any abnormality of pathological significance. Assessment of liver sample from OLZ groups showed Hepatic cell with ballooning degeneration, focal necrotic cell death and diffuse changes. Abnormality was detected in liver tissues. CFE100, CFE200, CFE400 with OLZ groups show normal hepatocytes arranged, with obvious sinusoids, and central vein no abnormality detected. The severity and incidence rate of the changes was reduced after treatment with CFE100, CFE200, CFE400 plus OLZ.

2011). The co-administration of CFE significantly mitigated these lipid disturbances. At doses of 200 and 400 mg/kg, CFE reduced the levels of TG, VLDL, LDL, and TC while increasing HDL. These findings suggest that CFE may enhance lipid metabolism and have lipid-lowering effects, as previously observed in studies where CFE improved lipid profiles in high-fat diet-induced models (Gujjala *et al.*, 2017). The underlying mechanisms may involve modulation of lipid-regulating enzymes and antioxidant pathways, which warrants further exploration.

Olanzapine treatment led to increased liver and adipose tissue weights, indicative of lipid accumulation and potential hepatotoxicity. This is consistent with reports of olanzapine-induced hepatic damage and fat deposition in various tissues (Gujjala *et al.*, 2016). However, co administration of CFE (100-400 mg/kg) significantly reduced both liver and adipose tissue weights, particularly at the highest dose. This suggests that CFE may have hepatoprotective effects and could prevent fat accumulation in adipose tissue, as demonstrated by its impact on hepatic lipid levels and structural integrity in previous studies (Gujjala *et al.*, 2016). These observations further support the potential of CFE as a therapeutic agent for managing olanzapine-induced metabolic disturbances.

Oxidative stress plays a crucial role in the pathogenesis of olanzapine-induced metabolic syndrome (Ardakanian A *et al.*, 2022). In the current study olanzapine treatment increased Malondialdehyde (MDA) levels, a marker of lipid peroxidation, and decreased Superoxide Dismutase (SOD) activity, an important antioxidant enzyme. These findings corroborate the oxidative damage observed in olanzapine-treated animals (Gujjala *et al.*, 2016, Ferno *et al.*, 2011). Co-administration of CFE significantly reduced MDA levels and increased SOD activity, demonstrating its antioxidant potential. The antioxidant effects of CFE may contribute to its protective role in mitigating oxidative damage and preventing the development of metabolic syndrome. Similar antioxidant properties of CFE have been observed in high-fat diet-induced models of oxidative stress (Ardakanian *et al.*, 2022). Histopathological examination of liver tissue revealed severe alterations in the hepatic architecture of olanzapine-treated rats, including ballooning degeneration, necrosis, and widespread cell death. These findings are in line with previous reports of hepatotoxicity associated with antipsychotic medications (Gujjala *et al.*, 2016). In contrast, rats co-treated with CFE exhibited preserved liver architecture, with less extensive tissue damage. These histopathological findings suggest that CFE may exert hepatoprotective effects, which could be attributed to its antioxidant properties and its ability to modulate lipid metabolism.

CONCLUSION

In conclusion, the results of the present study provide compelling evidence that *Caralluma fimbriata* extract (CFE) may effectively alleviate olanzapine-induced metabolic side effects, including weight gain, dyslipidemia, oxidative stress, and hepatotoxicity. The appetite-suppressing, lipid-lowering, and antioxidant properties of CFE suggest that it could be a valuable adjunctive therapy for managing olanzapine-induced metabolic syndrome. However, while these findings are promising, further clinical studies are required to validate these effects in humans and elucidate the precise molecular mechanisms through which CFE exerts its therapeutic actions. Additionally, future research should explore the interactions between CFE's secondary metabolites and the molecular targets involved in the regulation of metabolism and oxidative stress in the context of olanzapine-induced metabolic disturbances.

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ABBREVIATIONS

CFE: *Caralluma fimbriata* Extract; **OLZ:** Olanzapine; **TG:** Triglycerides; **TC:** Total cholesterol; **HDL:** High-density lipoprotein; **LDL:** Low-density lipoprotein; **VLDL:** Very-low-density lipoprotein; **GSH:** Glutathione; **CAT:** Catalase; **SOD:** Superoxide dismutase; **MDA:** Malondialdehyde.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ETHICAL STATEMENT

The study adhered to ethical guidelines as approved by the Institutional Animal Ethics Committee (IAEC) of Pravara Rural College of Pharmacy. The animals were provided with standard care conditions, including a regular diet and proper housing environment. All experimental procedures were conducted in compliance with CPCSEA regulations to ensure humane treatment of the animals throughout the research process.

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