RESEARCH ARTICLE

Effect of Corn Silk on Olanzapine Induced Obesity in Rat

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ABSTRACT

Background: Antipsychotics are recommended as the initial, treatment for schizophrenia and other psychotic disorders based on evidences. They are commonly prescribed for conditions like borderline personality disorder, obsessive-compulsive disorder, and forms of dementia including Alzheimer's disease. The effect of medications is limited due to side effects, those must be carefully balanced against their varying therapeutic benefits across these conditions.
Objective: To study effect of corn silk extract in olanzapine induced obesity in rats.
Methodology: Corn silk extract were made by reflux extraction method in which corn silk were collected at maturated stage, dried at room temperature and dry powder is refluxed in 70% ethanol, for 3 to 4 hour and after filtered and dry it. Six animals containing five groups were assigned. For 21 days dose (100, 200,400 mg/kg) were co-administered of CSE with olanzapine 2 mg/kg . Body weight, locomotor activity on day 1st and day 21st. On 21st day OGTT was conducted. Dissected organ weighed and collected visceral fat and estimation of lipid profile and calculate the oxidative stress of animals.
Result: Corn silk extract ameliorates obesity in rats induced by olanzapine and hyperphagia by improved lipid metabolism.
Keyword: Olanzapine, Lipid Metabolism, Corn Silk Extract, Weight Gain, Metabolic Changes
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INTRODUCTION

Antipsychotics are mainly indicated as treatment for schizophrenia; some are used for bipolar disorder, Tourette's disorder, etc. Because these medications' effectiveness is generally overshadowed by their side effects, it often needs to be weighed against their therapeutic benefit.[1] Therefore, discussions of antipsychotics are often dominated by side effects rather than their efficacy, with recommendations frequently to choose them on the basis of side effect profile rather than similar efficacy across various conditions.[1] Among the antipsychotics, olanzapine is atypical medicine mainly used in schizophrenic & bipolar condition. It is effective in both new-onset and long-term maintenance of schizophrenia and can be given orally or by intramuscular injection.[1] Common side effects like weight gain, movement disorders, and dry mouth. More severe ADR like orthostatic hypotension, neuroleptic malignant syndrome, high blood sugar levels, seizures. Olanzapine use in older adults with dementia give risk of death, its late pregnancy use can cause movement disorders in the newborn.[2]
Second-generation antipsychotics (SGAs) generally show less extrapyramidal symptoms compared to first-generation antipsychotics; however, they can still cause effects like weight gain and metabolic disturbances.[3] These metabolic changes are associated with increased morbidity due to conditions like hypertension and type II diabetes.[3] Notably, olanzapine and clozapine are especially recognized for causing substantial weight gain and metabolic issues. Approximately 86% patients treated with OLZ experience obesity over time. This weight gain can lead to further health complications such as dyslipidemia and diabetes.[3]
Metabolic effects induced by SGA are highly complex and involve CNS & PNS. One possible mechanism by which SGAs could exert their adverse metabolic effects, such as hyperlipidemia, is through increased enzymatic activity, resulting in increased lipogenesis.[4] Recently, natural compounds have been studied for their potential to counteract these effects. For example, berberine, an alkaloid in many herbs, has shown pharmacological effect like anti-obesity and anti-diabetic.[5]
Moreover, ginger have been reported to have potential in decreasing weight gain and increasing energy expenditure in animal models.[6] Curcumin has also been investigated for anti-obesity effects when combined with olanzapine treatment in rats.[6] Corn silk (Zea mays) has been used in traditional medicine in many cultures and contains many bioactive compounds with potential health-promoting activities, including antioxidative and anti-diabetic properties.[7] Its flavonoids show strong antioxidant activity by scavenging free radicals and interacting with cellular processes.[8]
Given the limited success in managing antipsychotic-induced weight gain with existing medications, this

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Table 1: Determination of preliminary test of phytoconstituents for CSE

Phytoconstituents	Results
Flavonoids	Positive
Alkaloids	Positive
Tannins	Positive
Phenolic compounds	Positive
Saponins	Positive
Carbohydrates	Positive

research aimed to study effect of CSE on body weight and metabolism in olanzapine treated female Sprague-Dawley rats.[9] The research focused on effects of extract on body weight regulation in relation to glucose and lipid metabolism in this animal model, thereby providing insights into new therapeutic strategies for obesity management associated with antipsychotic treatment.

MATERIALS AND METHODS

Plant and Reagents

Corn silk were collected in month of September. From Nashik district in Maharashtra and were authenticated from Padmashri Vikhe Patil College of Science, Arts and Commerce Pravaranagar, Tal.- Rahata, Dist.- Ahilyanagar. Chemical such as Olanzapine were brought from Yarrow chem. Product, Mumbai, India. Loba & Chemie Pvt. Ltd. provided Gallic acid, Folin-Ciocalteau reagent, Ferric chloride, etc. while Research lab fine chemicals industries, Mumbai, India provided Hydrogen peroxide, Disodium hydrogen phosphate, sodium citrate, etc.

Methodology

Hydroalcoholic extraction of Corn silk

Weighing 2000 gm of corn silk coarse powder after drying. Preparation of extraction by Reflux Extraction method for 3 hours.[10] Adjust temperature up to 50 to 60^0C. For extraction 70:30 ratio of alcohol and water used. mix with corn silk powder with alcohol and water transfer it into round bottom flask for extraction.

HR-LCMS Analysis of Plant extract

High-Resolution Liquid Chromatography and Mass Spectrometry (HRLCMS) analyzed Corn silk extract using an Agilent G6550A system.[11] The method involved mass range from 120-1200 Da, at one spectrum per second scanning rate.[11] The Metlin library facilitated the identification of constituents by comparing mass spectra, revealing insights into the chemical profile of Corn silk.

Pharmacological Evaluations

Experimental animals and approval

Healthy Sprague-Dawley female rats (180±10 gm) was utilized in study. Animals purchased from National Lacsmi BioFarm. Aundh Pune CCSEA Reg. Number: 1277/PO/RcBt/S/09/CCSEA, were housed in an optimal condition of temperature (22-25^0C), relative humidity (65-70%) and environment (12:12 light and dark cycle).[12] Animals were fed with standard diet. Distilled water was given ad libitum.[13] The reserch protocols were approved by the Institutional Animal Ethical Committee (IAEC) of pharmacology-II Laboratory. Pravara Rural College of Pharmacy. Pravaranagar CPCSEA Registration No. 1942/PO/Re/S/17/CCSEA/2023/01/05/01.

Animals (female SD rat) were randomly assigned to five groups as stated below,

Normal: Served as Vehicle (0.1 N HCL adjusted pH with 0.1 N NaOH) 2 ml/kg divided in two doses at 12hr interval.[14]

Table 2: Compound Determination of CSE by HR-LCMS

Phytoconstituents	Compound
Flavonoids	dihydroxy-4'-methoxyflavone, Isoswertisin, 4'-glucoside, 3,6-Diglucopyranosyl-5,7-Diosminm Peonidin-3-rhamnoside-5-glucoside, Maysin-3'-methyl ether, Isoswertisin-2''-O-rhamnoside, Biochanin A7-(6- methylmalonylglucoside
Terpenoids	Methyl-delta-ionone, delta-Methylionone, alpha-Irone, (+)-trans-alpha-Irone, 2-Oxo-5,11(13)-eudesmadien-12,8-olide, Xanthatin, Xerantholide, Zaluzanin C
Anthocyanin	Peonidin 3-rhamnoside 5-glucoside
Phenol	4-tert-Octylphenol, 2,4-Di-tert-butylphenol, propylphenol
Proteins	L-isoleucyl, L-proline
Volatile compounds	Prostaglandin I2

Table 3: Body weight gain (%) at different interval (Days) in rat treated with vehicle olanzapine (2mg/kg) OLZ + CSE (100,200,400).

Days/ Groups	3	6	9	12	15	18	21
Normal	0.09±0.09	1.26±0.0 9	2.62±0.2 0	4.07±0.26	5.56±0.33	6.72±0.33	8.18±0.34
Olanzapine	1.06±0.18	3.37±0.3 0 ****	6.84±0.2 7 ****	9.94±0.32 ****	14.31±0.7 8 ****	16.98±0.4 1 ****	19.49±0.2 1 ****
CSE100+OLZ	1.62±0.23 4	4.74±0.4 0 ##	7.07±0.2 7 ##	10.66±0.2 3 ####	12.60±0.2 6 ####	13.58±0.4 7 ####	15.51±0.1 1 ####
CSE200+OLZ	0.77±0.12	2.23±0.2 4 ##	3.46±0.5 3 ####	5.53±0.68 ####	6.98±0.73 ####	7.18±0.84 ####	8.73±0.82 ####
CSE400+OLZ	0.87±0.13	1.62±0.0 9 ####	2.73±0.2 9 ####	3.42±0.23 ####	4.40±0.33 ####	4.69±0.50 ####	5.43±0.28 ####

All the data are represented in mean ± SEM **** $p < 0.0001$ compared to normal ## $p<0.01$, #### $p<0.0001$ compared to Olanzapine

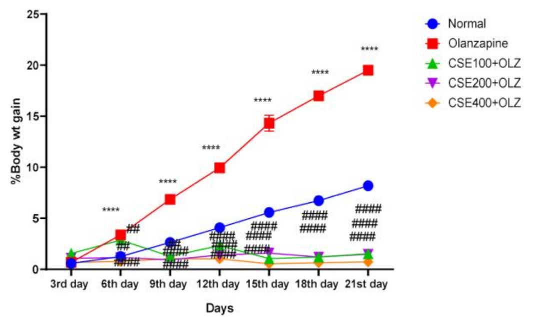

Figure 1: Body weight gain (%) at different intervals (Days) in rats treated with vehicle olanzapine (2 mg/kg/day), OLZ + CSE (100,200,400 mg/kg/day). **** p

Olanzapine: Served as olanzapine injected by 2mg/kg/day, divided in 2 doses at 12hr interval i.p administration for 21 days.[14]

CSE 100 +OLZ: Served as olanzapine injected by 2mg/kg/day, i.p. divided in 2 dose .at 12hr interval + CSE extract 100mg/kg one dose orally administration for 21 days.

CSE 200 + OLZ: Served as olanzapine injected by 2mg/kg/day, i.p. divided in 2 doses at 12hr interval + CSE extract 200mg/kg one dose orally administration for 21 days.

CSE 400 + OLZ: Served as olanzapine injected by 2mg/kg/day, i.p. divided in 2 doses at 12hr interval + CSE extract 400mg/kg one dose orally administration for 21 days.

During study, body weight was monitored daily. An oral glucose intolerance test was conducted on the 22nd day. Blood samples collected via retro-orbital route for analysis. At study's end, organs (liver, kidney, heart) were harvested, weighed, and preserved for further analysis.[15,16]

Locomotor activity

Locomotor behavior of animal was examined by Y-Maze apparatus, briefly individual animals were placed in Y-Maze arm of 35 cm-long, 25cm-high, 10cm-wide arms for two minute as after 30 min locomotor activity was recorded i.e., travelled distance in millimeter after drug administration.[17]

Oral glucose tolerance test (OGTT)

On overnight fasted animals OGTT was performed. Equal volume vehicle is given to normal rats. Olanzapine rats in group II-V administered ACD p.o. As 30 min. of extract given glucose (2g/kg; p.o.) was fed.[18] From retro orbital plexus blood was withdrawn at 30, 60, 90 and 120 min as estimated.[19]

Biochemical parameters

Blood was collected from the retro-orbital route in clean Eppendorf apparatus on 21st day. Following coagulation, samples centrifuged 4000 rpm, 4^0C for 5 min. Separated serum stored at -20 ^{0}C till the estimation of biochemical parameters.[20]

Measuring the amounts of serum TG

Overnight fasted animals were sacrificed after. Then serum samples were delivered to laboratory to check amounts of Triglycerides (TG).[21] TG used in kit Transasia bio- medicals Ltd.

Measuring the amounts of serum TC

Overnight fasted animals were sacrificed after. Then serum samples were delivered to laboratory to check amounts of TC (AUTOSPAN Liquid Gold Cholesterol 4000029011).

Measuring the amounts of serum HDL

Overnight fasted animals were sacrificed after. Then serum samples were delivered to laboratory to check amounts of HDL (HDL Cholesterol Direct estimation kit PBHDL-23092

Measuring the malondialdehyde (MDA) in liver tissue

In 5ml microtube approx. 200 mg of each liver sample were kept in ice at start of experiment, and 10% tissue homogenate is created by adding 1.15% KCL. Next, the homogenate of tissue was vortexed, approximately 500 µl of homogenized tissue were kept in glass tube, in which 1 ml 0.6% TBA and 3 ml 1% phosphoric acid were added. In hot water those tubes were submerged. After that, each cooled sample receives 4 milliliters of butanol, and it is vortexed for a minute.[22,23]

Measuring glutathione (GSH) in liver tissue

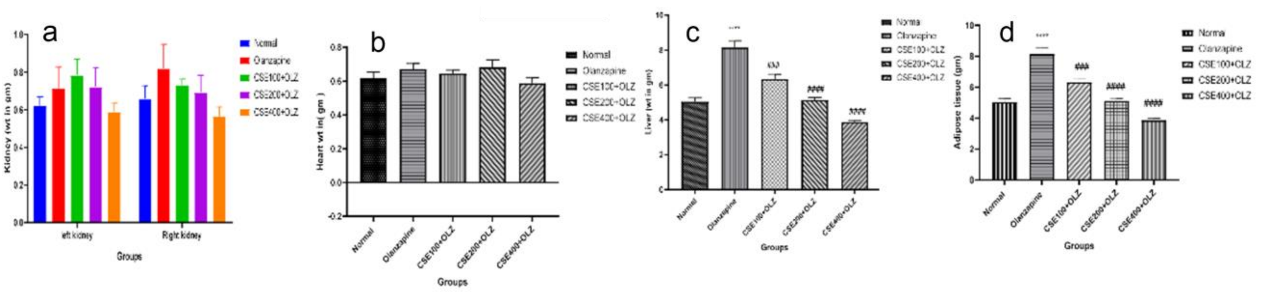

Figure 2: Effect on organ weight; (a) Liver (gm) in rats treated with vehicle olanzapine (2mg/kg/day), OLZ+CSE (100,200,400 mg/kg/day). ****p<0.0001 compared to normal, #### p <0.0001 compared to Olanzapine. There was significant decreased in liver wt as compare to olanzapine treated group. (b) Heart (gm) in rats treated with vehicle olanzapine (2 mg/kg/day), OLZ+ CSE (100,200,400 mg/kg/day). There was no any significant effect observe on heart compare to olanzapine treated group. (c) Kidney (gm) in rats treated with vehicle Olanzapine (2 mg/kg/day), OLZ + CSE (100,200,400 mg/kg/day). (d) Adipose tissue in rats treated with vehicle olanzapine (2 mg/kg/day), OLZ + CSE (100,200,400 mg/kg/day). ****p <0.0001 compared to normal, #### p <0.0001 compared to Olanzapine. According to above result it has been showed that weight of adipose tissue in normal and CSE treated rat are less than olanzapine treated group.

Table 4: Organ weight rats treated with vehicle Olanzapine (2 mg/kg/day), OLZ + CSE (100,200,400 mg/kg/day)

Groups	Liver (gm)	Heart (gm)	Adipose Tissue (gm)	Kidney (gm)
Normal	5.03 ± 0.22	0.61 ± 0.03	5.03 ± 0.22	0.64 ± 0.01
Olanzapine	8.14 ± 0.38 ****	0.67 ± 0.32	8.14 ± 0.38 ####	0.76 ± 0.05
CSE100+OLZ	6.33 ± 0.25 ###	0.64 ± 0.01	6.33 ± 0.25 ###	0.75 ± 0.02
CSE200+OLZ	5.12 ± 1.15 ####	0.68 ± 0.04	5.12 ± 0.15 ####	0.70 ± 0.01
CSE400+OLZ	3.86 ± 0.11 ####	0.58 ± 0.03	3.86 ± 0.11 ####	0.57 ± 0.01

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

Table 5: Lipid profile in rats treated with vehicle Capitoline (2 mg/kg/day),OLZ + CSE (100,200,400 mg/kg/day)

Groups	Triglyceride (mg/dl)	Cholesterol (mg/dl)	HDL (mg/dl)	LDL (mg/dl)	VLDL (mg/dl)
Normal	40.58 ± 1.82	46.21 ± 1.50	41.77 ± 0.56	-3.51 ± 1.98	8.11 ± 0.36
Olanzapine	88.19 ± 3.43 ****	62.61 ± 0.98	25.32 ± 1.12	19.54 ± 1.41 ****	17.64 ± 0.68 ****
CSE100+OLZ	63.13 ± 8.36 #	41.28 ± 0.85	35.11 ± 1.34	-6.46 ± 2.46 ##	12.63 ± 1.67 #
CSE200+OLZ	50.02 ± 4.73 ####	37.59 ± 0.94	29.66 ±0.70	-2.02 ± 1.75 ##	10.01 ± 0.94 ####
CSE400+OLZ	48.39 ± 2.47 ####	32.24 ± 1.46	28.12 ± 1.65	-5.56 ± 1.75 ##	9.67 ± 0.49 ####

All data are represented in mean ± SEM (n = 6), **** p <0.0001, *** p <0.001, ** p <0.01, * p<0.05 compared to normal, # p <0.05 ## p <0.001, ### p <0.001, #### p <0.0001 compared olanzapine.

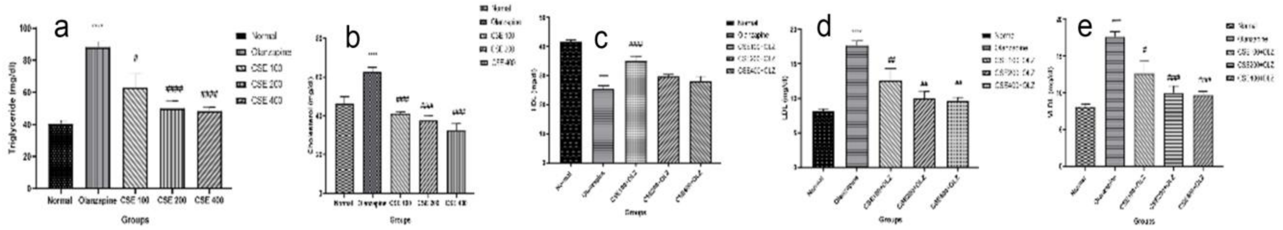

Figure 3 (a), (b), (c), (d); Effect of CSE on lipid profile: (a) Triglyceride (mg/dl) in rats treated with vehicle Olanzapine (2 mg/kg/day), OLZ+ CSE (100,200,400 mg/kg/day). ****p <0.0001 compared to normal, # p <0.05 , <0.001, #### p <0.001 compared to Olanzapine . According to result obtained it is observed that there was significant decreased in TG level as compare to olanzapine treated group. (b) Cholesterol (mg/dl) in rats treated with vehicle Olanzapine (2 mg/kg/day), OLZ+ CSE (100,200,400 mg/kg/day). **** p <0.0001 compared to normal, #### p <0.0001, #### p <0.0001 compared to Olanzapine. According to result obtained TC of extract treated group are significantly decreased as compare to olanzapine treated group. (c) High density lipoprotein (mg/dl) in rats treated with vehicle Olanzapine(2mg/kg/day), OLZ + CSE (100,200,400 mg/kg/day). ****p <0.0001 compared to normal, #### p <0.0001 #### p <0.0001, compared to Olanzapine. Above data indicate that only 100mg CSE show significant effect on HDL as compare to olanzapine. (d) Low density lipoprotein (mg/dl) in rats treated with vehicle olanzapine (2mg/kg/day), OLZ plus CSE (100,200,400 mg/kg/day). ****p <0.0001 compared to normal, ##p <0.01, compared to Olanzapine. There was significantly similar effect of each group of CSE as compare to olanzapine treated group. (e) Very Low-density lipoprotein(mg/dl) in rats treated with vehicle olanzapine (2 mg/kg/day), OLZ + CSE (100,200,400 mg/kg/day). ****p <0.0001 compared to normal, # p <0.05, ### p <0.001, compared to olanzapine. Significantly effect on 200 and 400 mg/kg CSE treated animal show effect on VLDL level as compare to olanzapine treated group.

To examine reaction between sulfhydryl groups and DTNB, resulting in colored complex with absorption at 412 nm. Liver samples (200 mg) were homogenized with buffer (pH 7.4) for 10% tissue homogenate. Following centrifugation, supernatant is mixed with buffer (pH 8) and DTNB, leading to a yellow color formation. Absorbance is measured at 412 nm, and GSH concentration is quantified as nmol/g tissue using a standard curve. The blank solution consists of DTNB, TCA, and phosphate buffers.[24,25]

Measuring Catalase (CAT) in liver tissue

Buffer (pH 7) 1.0 ml (50 mM) and 0.1 ml H_2O_2 (30 mM) was mixed with 50 pl. of supernatant to measure catalase activity. For thirty seconds, the absorbance was measured every five seconds with a spectrophotometer, paying particular attention to the reaction's decreasing slope. At 240 nm. absorbance readings were obtained. [26]

Measuring Superoxide dismutase (SOD) in liver tissue

During the enzyme activity assay, 640 µL water. 10 µL Triton X-100 (0.3%), 100 µL EDTA (1mM), 100 µl NBT (240µM) and 25 L of tissue supernatant were combined with the mixture. mM hydroxylamine. At intervals of one

Table 6: Locomotor activity in rats treated with vehicle Olanzapine (2mg/kg/day), Olanzapine+ CSE (100,200,400 mg/kg/day)

Groups	Day 1st Travelled distance (mm)	Day 21st Travelled distance (mm)
Normal	32.96 ± 34.16	48.83 ± 55.97
Olanzapine	25.96 ± 14.38	55.16 ± 79.97 ****
CSE100+OLZ	25.41 ± 23.27	19.33 ± 18.89
CSE200+OLZ	29.33 ± 58.17	37.25± 26.85 ####
CSE400+OLZ	27.50 ± 63.50	40.75 ± 16.26 ####

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

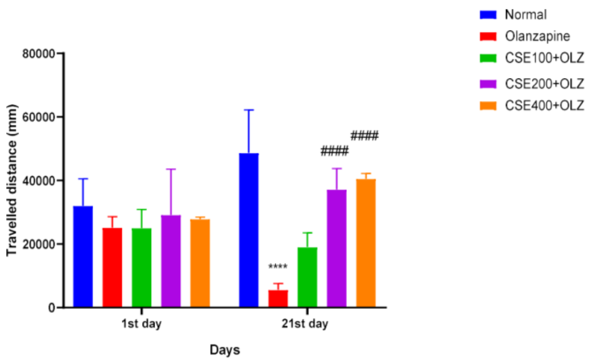

Fig. 4. Locomotor activity in travelled distance(mm) in rats treated with vehicle olanzapine (2 mg/kg/day), OLZ + CSE (100,200,400 mg/kg/day). ****p <0.0001 compared to normal, ####p <0.0001, compared to Olanzapine. CSE treated shows significant effect on day 21st as compare to olanzapine treated group in locomotor.

minute to three minutes, the spectrophotometric readings were taken in kinetic mode at a wavelength of 560 nm in order to track the reaction's rising slope. Units (U) per gram of tissue corresponded to the enzyme activity.[27]

Histopathological studies

For the correct fixing, small sections of liver tissue were collected within 10% neutral formalin. On Paraffin wax tissues were embedded. Hematoxylin and eosin used as stain that had been cut, mounted, and stained to a thickness of 5 mm. Microscopic examination of sections was assessed using a 4-point scale and percentage of lesion involved in the tissue section and as: 0=No Abnormality detected (NAD)/Within Normal Limit (WNL), 1= Less (0-10%), 2= Medium (11-20%), 3= Moderate (21-40%) and 4=Severe (41-100%).[28]

RESULTS

Extraction and Phytochemical investigation

Yield of CSE was 3.025% w/w per 100 gm. The phytochemical analysis given in Table 1.

HR-LCMS of CSE

Approximately 62,000 recognized chemicals record found. The standard spectra of recognized constituents found in Metlin library were compared with spectra of unidentified constituents of silk extract. Some important HR-LCMS results given in Table 2.

Weight gain by Olanzapine

Weight gain (%) is higher ($p < 0.0001$, F=17.97) in Olanzapine treated compared to Normal. Gain was significant ($p < 0.0001$) from 6th to 21st day. Co-administration of CSE at dosage of 100, 200 and 400 (mg/kg) with Olanzapine reduction ($p < 0.001$) As predicted in Figure. 1. and Table 3.

Effect on organ weight

Capitoline treated group is a significantly higher weight of liver and adipose tissue compared to normal and non-significant difference in heart and kidney weight. As predicted in Fig. 2. & Table 4.

Effect of CSE on lipid profile

Difference in TG ($p < 0.0001$, F = 15.38, R2 0.7111), TC ($p < 0.0001$, F = 96.23, R2 0.9390), HDL ($p < 0.0001$, F = 32.22, R2 0.8375), LDL ($p < 0.0001$, F = 32.12, R2 0.8371), VLDL ($p < 0.0001$, F = 15.38, R2 0.7110) among groups. There was induction in TG, total cholesterol, LDL, and VLDL and reduction in HDL in Capitoline group. Co-administration of CSE at dose 200, 400 mg/kg showed increase in HDL level and reduced TG and VLDL compared to Capitoline. Similarly, co-administration of CSW with Olanzapine reduced LDL level and total cholesterol at 100, 200, and 400 mg/kg compared to olanzapine. As predicted in Table 5 and Fig. 3.

Effect on locomotor activity

Time dependent travelled distance in locomotor after co-administration of CSE with Olanzapine observed. On 21st day reduction in locomotor in Olanzapine group observed. Co-administration of CSE (200, 400 mg/kg) with Olanzapine showed reduction of locomotor activity induced by Capitoline. Shown in Table 6 and Fig. 4.

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

Fig. 5(a) indicates, Olanzapine treated rats have non-significant the amount of CAT in liver tissue compared to normal. CSE in varying doses (100, 200, 400 mg/kg) combined with olanzapine, MDA levels were lowered ($P<0.01$) than olanzapine group in Fig. 5(b). Fig. 5 (c) indicates that Olanzapine treated rats significant decrease the amount of SOD in liver tissues compared to normal. Fig. 5 (d) indicates that Olanzapine treated rats' have significant amount of GSH in liver tissue compared to normal. Summarized in Table 7.

Effect on CSE on oral glucose tolerance test

OGTT time-dependent and group dependent no significant difference in blood glucose found. Significant difference in total AUC of glucose of groups found. Fasting glucose level and AUC for OGTT of Olanzapine treated rats were non-significant. As in Fig. 6.

Effect on histopathology study of Liver

In histopathology study exhibited a normal hepatocyte arranged in cords obvious sinusoids no abnormality was observed in liver tissues of OLZ with CSE administered group of animals compared to liver tissues of olanzapine group of animals. Given in Fig. 7.

DISCUSSION

Table 7: Oxidative stress indicator in rats treated with vehicle olanzapine(2mg/kg/day), OLZ plus CSE (100,200,400 mg/kg/day).

Groups	Groups MDA (nmol/gm/gm of tissue)	CAT (micromole of H_2O_2/gm of tissue)	SOD (unit/gm of tissue)	GSH (micro gm/gm of tissue)
Normal	28.62 ± 3.01	7.96 ± 0.14	0.32 ± 0.07	1275 ± 75.95
Olanzapine	53.54 ± 6.40***	7.71 ± 0.007	0.57 ± 0.07	824.5 ± 18.34 ***
CSE100+OLZ	56.48 ± 2.58	7.73 ± 0.01	0.31 ± 0.12	905.5 ± 16.66
CSE200+OLZ	36.09 ± 1.32##	7.76 ± 0.09	0.29 ± 0.08	947.5 ± 14.37
CSE400+OLZ	28.98 ± 0.62###	7.80 ± 0.04	-0.11 ± 0.10	1097 ± 41.37 ####

All data are represented in mean ± SEM (n = 6),* p <0.05,*** p <0.001compared to normal, ## p <0.01, ### p <0.001 , #### p <0.0001 compared to Olanzapine.

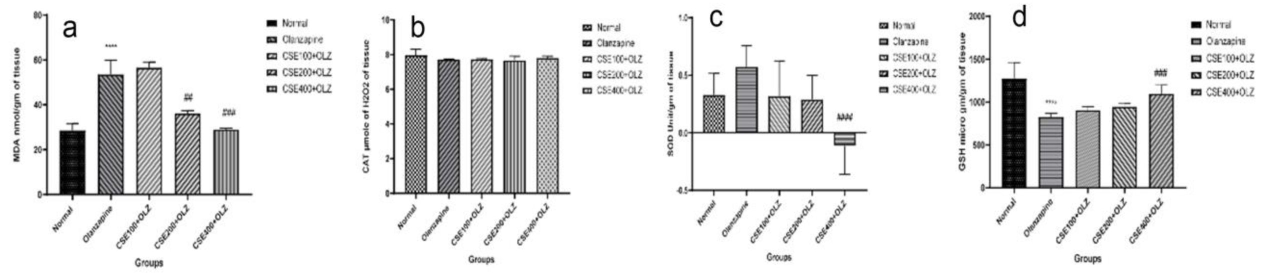

Figure 5 (a), (b), (c), (d): Effect on MDA, GSH, CAT and SOD levels of liver tissue; (a) Malondialdehyde (nmol /gm of tissue) in rats treated with vehicle olanzapine (2 mg/kg/day), OLZ + CSE (100,200,400 mg/kg/day). **** p <0.0001 compared to normal, ## p <0.01, ### p<0.001 compared to Olanzapine. There was significant effect of CSE 200 400mg/kg these show significant decreased in MDA level. (b) Catalase (micromole of H2O2 /gm of tissue) in rats treated with vehicle olanzapine (2 mg/kg/day), OLZ +CSE (100,200,400 mg/kg/day). There was no any significant effect of CSE on CAT level as per above graph. (c) SOD (Unit /gm of tissue) in rats treated with vehicle Olanzapine (2mg/kg/day), +CSE (100,200,400 mg/kg/day). The level of SOD 400 mg/kg CSE were significantly decreased as compare to olanzapine group, #### P<0.0001. (d) Glutathione (micro gm/gm of tissue) in rats treated with vehicle olanzapine (2 mg/kg/day), OLZ plus CSE (100,200,400 mg/kg/day). ***p <0.001 compared to normal, ###p <0.001, compared to Olanzapine. There was significant effect of CSE 400mg/kg in which increased in GSH level.

With insights from prior research, olanzapine at dose of 2 mg/kg for 21 days rise to significant increase in body weight, accompanied by increased food intake (hyperphagia).[29] These medications can also produce anorexigenic effects, raising concerns about the safety of psychotropic treatments.[30] Ongoing efforts aim to develop adjunctive therapies to mitigate the metabolic side effects associated with antipsychotics like olanzapine.

The mechanisms behind olanzapine-induced weight gain remain partially understood.[9,31] Olanzapine (2 mg/kg/day IP) was given to Sprague-Dawley female rats over 21 days. Parameters such as body weight, locomotor activity, oral glucose tolerance tests, lipid profiles, organ weights post-dissection, histopathological changes in the liver and kidneys, and oxidative stress markers were assessed simultaneously.

Olanzapine resulted in weight (10% body weight) compared to control (3.15% weight) across various doses and routes in animals.[32] Male rats administered 5 mg/kg olanzapine via IP for 11 days, increases in body weight, were noted alongside dyslipidemia and hyperglycemia.[33] Metabolic disturbances were observed in female Sprague-Dawley rats.[33] These findings suggest that herbal extracts may effectively reduce body weight and food intake while increasing water intake in corn silk extract-treated rats receiving olanzapine at dose of 2 mg/kg.[32]

Interestingly, treatment with corn silk extract did not significantly affect kidney or heart weights but showed reduction in overall weight of rats.[34] The link between olanzapine treatment and increased body fat was also evident from liver weight changes post-treatment.[32] This study establishes a positive correlation between white adipose tissue fat accumulation and body weight gain due to olanzapine's influence on enhancing white fat deposition.[35] Additionally, olanzapine facilitates triglyceride accumulation and differentiation of preadipocytes into mature adipocytes in vitro.[35]

Carnitine palmitoyltransferase-1 (CPT-1) plays a crucial role in regulating beta-oxidation by controlling acylcarnitine transport into mitochondria and is vital in managing metabolic disorders.[36] We also assessed corn silk extract's impact on liver weights; administration of extract of corn silk at dose 200 and 400 mg/kg resulted in marked reductions, overall organ weights remained stable except for liver weights.[37]

Corn silk extract improved lipid metabolites among olanzapine-treated rats by decreasing total cholesterol, triglycerides, and LDL cholesterol levels.[38] Abdominal obesity is often associated with dyslipidemia characterized by elevated triglycerides essentially linked to ectopic lipid accumulation in the liver contributing to conditions such as diabetes mellitus and metabolic syndrome.[39] High levels of

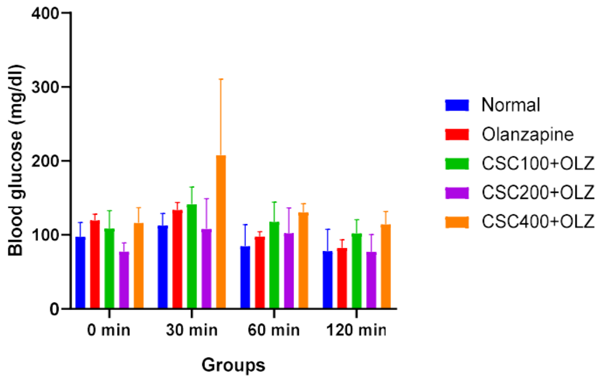

Figure 6: OGTT in AUC in rats treated with vehicle Olanzapine (2 mg/kg/day), OLZ+CSE (100,200,400 mg/kg/day)

cholesterol, triglycerides, and LDL are risk of coronary disease. Findings indicate that olanzapine elevates cholesterol levels alongside triglycerides and HDL/LDL cholesterol.[40,41]

Malondialdehyde (MDA), a marker for oxidative stress resulting from lipid peroxidation within cells and tissues, is produced through excessive free radical formation due to oxidative stress.[42] MDA readily interacts with various functional groups including DNA and proteins.[43] The current study noted a significant increase (<0.0001) in MDA levels among rats treated with olanzapine due to oxidative stress linked to obesity and an inability to scavenge free radicals effectively. However, there was decrease in MDA levels among those treated with corn silk extract at dose 200 and 400 mg/kg.

In study, SOD activity in liver tissue did not show significant changes; however, CAT activity was notably enhanced compared to olanzapine-treated rats. The current findings demonstrate effect ($P<0.0001$) of CSE at dosage of 400 mg/kg relative to those treated with olanzapine alone. Corn silk extract has been recognized for its potential antioxidant properties and ability to modulate oxidative parameters such as CAT activity under conditions associated with oxidative stress like obesity.[44]

While specific studies directly examining corn silk extract's effect on GSH levels during obesity are limited, existing research suggests that antioxidant-rich natural extracts typically lead to an increase rather than a decrease in GSH levels due to its essential role in cellular defense against oxidative stress supporting its synthesis through antioxidant-rich compounds.

CONCLUSION

The study investigates the effects of CSE on olanzapine-induced obesity, highlighting the significant weight gain and metabolic disturbances associated with OLZ treatment. Results indicate that corn silk extract effectively mitigates these adverse effects, leading to improved body weight regulation and lipid metabolism. The extract demonstrated a notable reduction in body weight gain and alterations in lipid profiles, suggesting its potential as a therapeutic agent against antipsychotic-induced obesity. Furthermore, the research underscores the importance of exploring natural

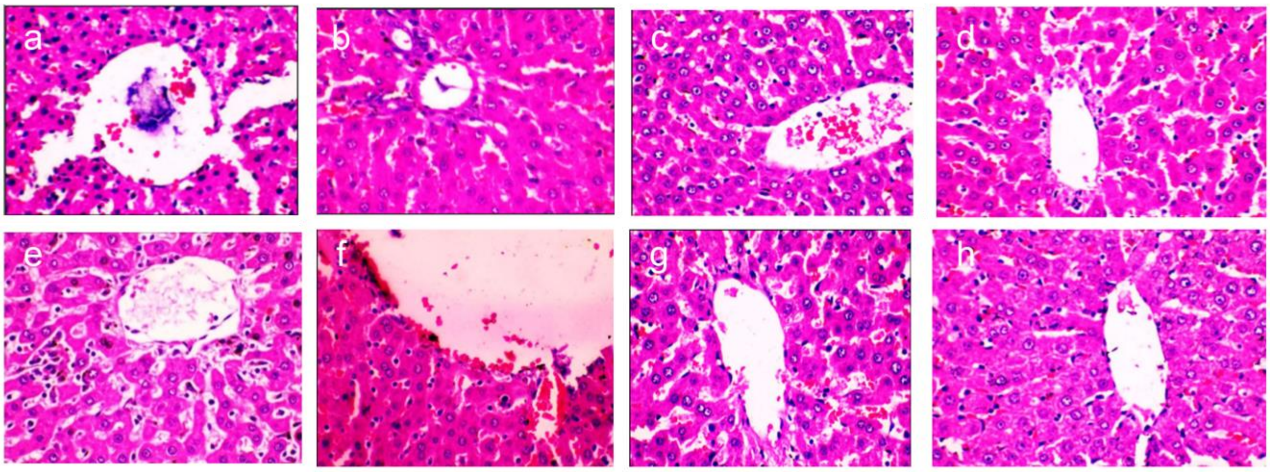

Figure 7 (a), (b), (c), (d), (e), (f), (g), (h): Histopathology study of Liver; (a) Normal Group (Animal 1) Normal hepatocytes arranged in cords, obvious sinusoids. No ab detected. 40X, H&E Strain; (b) Normal Group (Animal 2) Exhibited a normal hepatocyte arranged in cords, obvious sinusoids. No abnormality detected. 40X, H&E Strain; (c) Olanzapine Group (Animal 1) olanzapine injected by 2mg/kg/day i.p. Hepatic cells with ballooning degeneration, focal necrotic cell death, and diffuse changes. Abnormality detected. 40X, H&E Strain; (d) Olanzapine Group (Animal 2) olanzapine injected by 2mg/kg/day i.p. Hepatocytes with ballooning, focal necrotic cell death, diffuse changes and degeneration. Abnormality detected. 40X, H&E Strain; (e) CSE100+OLZ (Animal 1) olanzapine injected by 2mg/kg/day i.p. + CSE extract 100 mg/kg p.o. Exhibited a normal hepatocyte arranged in cords, obvious sinusoids. Mild abnormality and Mild hemorrhage detected .40X, H&E Strain; (f) CSE100+OLZ (Animal 2) olanzapine injected by 2mg/kg/day i.p. + CSE 100 mg/kg p.o. Exhibited a normal hepatocyte arranged in cords, obvious sinusoids. No abnormality detected. 40X, H&E Strain; (g) CSE200+OLZ (Animal 1) olanzapine injected by 2mg/kg/day i.p. + CSE 200 mg/kg p.o. Showing normal hepatic cells arranged in cords, clear sinusoids.40X, H&E Strain; (h) CSE200+OLZ (Animal 1) olanzapine injected by 2 mg/kg/day i.p. + CSE extract 200 mg/kg p.o. Showing normal hepatic cells arranged in cords, clear sinusoids.40X, H &E Strain.

compounds to counteract the side effects of antipsychotic medications. Overall, corn silk extract presents a promising avenue for managing metabolic issues linked to antipsychotic treatments. Future studies could further elucidate its mechanisms and efficacy in clinical settings.

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