

Pharmacological Evaluation of *Delonix regia* Extract on Clozapine-Induced Body Weight Gain and Lipid Metabolism in SD Female Rats.

¹Sagar Vaidya ,²Manish Ahire* , ³Monali Shelar ,⁴Tejas Jejurkar ,⁵Madhuri Harde

^{1,2,5}Assistant professor ,JES SND institute of pharmacy Babhulgaon Yeola Nashik -423401

³M pharm ,Department of pharmacology ,Matoshree institute of pharmacy Dhanore Yeola Nashik -423401

⁴Mrs.Saraswati Wani college of pharmacy ,Ganegaon ,Rahuri 413706.

Abstract: Second-generation antipsychotics like Clozapine are frequently used to treat bipolar disorder and schizophrenia, but they also have serious metabolic side effects include weight gain and dyslipidemia. The purpose of this study is to assess the pharmacological potential of *Delonix regia* (DLR) extract in reducing lipid abnormalities and body weight gain caused by Clozapine in female Sprague-Dawley (SD) rats. A total of five groups of female rats were randomly assigned: control, Clozapine treated, Clozapine + DLR extract-treated, . For 21 days, the *Delonix regia* extract was given orally at a dose of 100, 200 and 400 mg/kg/day, whereas clozapine was given at a dose of 2 mg/kg/day. Periodically, measurements were made of body weight, food consumption, and lipid profile parameters (total cholesterol, triglycerides, HDL, and LDL). Hepatic lipid buildup was also evaluated by histopathologically analyzing liver tissue. In comparison to the clozapine -only group, the results showed that co-administration of DLR extract significantly decreased clozapine -induced weight gain and improved serum lipid profiles. Histological results confirmed that *Delonix regia* had a protective impact on liver morphology. According to these results, *Delonix regia* may present a viable herbal remedy to lessen the metabolic side effects brought on by antipsychotics, therefore improving the long-term safety profile of clozapine treatment.

Keywords: *Delonix regia*, Clozapine , Weight gain, Lipid metabolism, Sprague-Dawley rats, Antipsychotic-induced dyslipidemia.

Introduction : While atypical antipsychotics are a mainstay of psychiatric pharmacotherapy for the treatment of schizophrenia and psychiatric illnesses, severe metabolic adverse effects, including insulin resistance, diabetes, and obesity, especially from clozapine and olanzapine, have attracted increasing concern. These adverse effects could lead to increased morbidity and

mortality and impair drug adherence and quality of life for patients. In recent years, Researchers have proposed several potential mechanisms for atypical antipsychotic-induced weight gain, including modulation of neurotransmitter action at the central level and involvement of body weight regulatory hormones such as leptin and ghrelin, resulting in increased appetite and reduced ability to perceive the feeling of satiety. The metabolic challenges faced by patients with schizophrenia (SCZ) impose significant burdens on themselves, their families, and society at large ^[1]. These metabolic disturbances are frequently associated with the use of antipsychotic medications ^[2]. Initially, the introduction of antipsychotics represented a breakthrough in managing SCZ symptoms and reducing recurrent hospitalizations ^[3]. Currently, the first-line antipsychotics in clinical practice are second-generation antipsychotics, including Clozapine (CLO), risperidone, collectively known as atypical antipsychotic drugs (AAPD), which exhibit excellent efficacy. Unfortunately, some AAPDs are also associated with metabolic side effects, such as weight gain, hyperglycemia, dyslipidemia, and cardiovascular complications ^[4]. Clozapine, a widely prescribed second-generation antipsychotic, has been clinically linked to significant metabolic side effects, particularly weight gain and dyslipidemia. These adverse effects not only reduce medication adherence but also contribute to long-term comorbidities such as type 2 diabetes, cardiovascular disease, and hepatic steatosis. Globally, the incidence of antipsychotic-induced weight gain is reported in up to 80% of patients within the first year of treatment, disproportionately affecting female patients.

Table no 1 :Taxonomical classification of *Delonix regia*

Kingdom	Plantae
Division	Magnoliophyta
Subdivision	Spermatophyta
Class	Magnoliopsida
Subclass	Rosidae
Order	Fabales
Family	Fabaceae
Genus	Delonix
Species	<i>Delonix regia</i>

Delonix is a genus of flowering plants in the pea family, Fabaceae and subfamily Caesalpinioideae. This genus contains trees that are native to Madagascar and East Africa. By far the best known species is the Royal Poinciana (*D. regia*). The name of the genus is derived from the Greek words 'delos' meaning 'evident,' and 'onyx' meaning "claw," that refers to the petals^[1]. *Delonix* erect unarmed tree. Leaves are abruptly bipinnate, leaflets are many but small and stipules are small. Flowers are large, showy, in terminal corymbs, bracts small. Calyx tube is very short, 5 lobes, valvate and subequal. Petals are 5, orbicular, imbricate, clawed, subequal. Margins are fimbriate. Stamens are 10 free, declinate, longexserted. Filaments are villous below and anthers are uniform. Ovary is sessile, many ovuled. Style filiform and stigma truncate, ciliolate.

The present study aims to evaluate the pharmacological effect of *Delonix regia* extract on body weight gain and lipid metabolic alterations induced by chronic Clozapine administration in SD female rats. Specific objectives include assessing changes in serum lipid profile, hepatic lipid accumulation, and associated behavioral and histopathological parameters. The study is designed to address existing therapeutic gaps by validating a safe, plant-based alternative to manage antipsychotic-induced metabolic disturbances.

Phytoconstituents : i. Stem bark: Flavanoids, alkaloids, saponins, sterols, stigmasterols, carotene, hydrocarbons phytotoxins, beta sitosterol, lupeol, p-methoxybenzaldehyde, isolupeol, carotene, phenolic acids.^[10,11] ii. Root bark: Glycosides, tannins, alkaloids, sterols, terpenoids and carbohydrates.^[12] iii. Flowers: Flavanoids, tannins, alkaloids, saponins,steroids,carotenoids [lycopene, phytoene,beta carotene,prolycopene,neolycopene],phenolic acid[gallic acid, protocatechuic acid, salicylic acid, transcinammic acid and chlorogenic acid], anthocyanins [cyanidin-3-glucoside and cyanidin-3-gentiobioside and beta sitosterol.



Fig no :1 *Delonix regia*

Materials and methods :**Materials**

Clozapine (API grade) was procured from a certified pharmaceutical supplier. Biochemical assay kits for lipid profile parameters (total cholesterol, triglycerides, HDL, LDL, and VLDL) were obtained from Erba Mannheim, Germany. Assay kits for oxidative stress markers (MDA, SOD, CAT, GSH) were purchased from Elabscience, USA. All chemicals and reagents used for phytochemical screening and experimental procedures, including ethanol, formalin (10%), normal saline, and glucose for OGTT, were of analytical grade and sourced from HiMedia Laboratories Pvt. Ltd., India.

Methods**Collection, Authentication, and Preparation of Plant Material**

The plant *Delonix regia* L. was collected during the month of September at its peak maturity stage to ensure optimal phytochemical content. A herbarium specimen of the plant was prepared according to standard botanical documentation protocols. This specimen was authenticated by JES SND college of science college Babhulgaon Yeola .

Extraction of Plant Material**Preparation of *Delonix regia* Aqueous Extract :-**

A hundred grams of powdered fruit was extracted for aqueous extraction using distilled water (200 mL) in the Soxhlet extraction method for 12 h. Using a rotating evaporator at 40 °C and reduced heat, the extract was almost completely evaporated (gummy residue). It was found that the yield was 12 percent. The gum residue was dissolved in a sufficient quantity of sterile water and preserved at a temperature of –20 °C before use^[16].

Dose Selection

An acute oral toxicity study of the hydroalcoholic extract of *Delonix regia*. was conducted in Wistar albino rats following OECD guideline 423. A single dose of 2000 mg/kg was administered orally, and no signs of toxicity, behavioral changes, or mortality were observed over a 14-day period, confirming the extract's safety at this level. Based on these findings, doses of ,100,200 and 400 mg/kg were selected for the pharmacological study to ensure efficacy assessment within a safe and well-tolerated range.

Experimental Animals

Female Sprague-Dawley rats weighing 180 ± 10 g were procured from National Lacsmi BioFarm, Aundh, Pune (CCSEA Registration Number: 1277/PO/RcBt/S/09/CCSEA). The animals were housed under controlled environmental conditions (temperature 22–25°C, relative humidity 65–70%) with a 12:12-hour light-dark cycle. They were provided with standard pellet diet and water ad libitum throughout the study period.

Experimental Design and Grouping

The study was designed to assess the protective effects of *Delonix regia* extract against Clozapine-induced metabolic alterations. Following an acclimatization period, female Sprague-Dawley rats were randomly divided into five groups (n = 5 per group). Group I (normal control) received the vehicle (0.1 N HCl neutralized with 0.1 N NaOH) intraperitoneally in two equal doses at 12-hour intervals. Group II (disease control) was administered Clozapine 2mg/kg divided into 2 dose /day i.p, split into two doses 12 hours apart, for 21 consecutive days. Group III (Test I) in which Clozapine 2mg/kg divided into 2 dose /day i.p + DLR 100mg/kg/day p.o. Group IV (Test II) in which Clozapine 2mg/kg divided into 2 dose /day i.p + DLR 100mg/kg/day p.o and Group V (Test III) in which Clozapine 2mg/kg divided into 2 dose /day i.p + DLR 400mg/kg/day p.o

Body weight, food intake were monitored daily, and assessed on days 1 and 21. On day 22, an oral glucose tolerance test (OGTT) was performed with glucose levels recorded at 0, 30, 60, and 120 minutes, followed by retro-orbital blood collection for lipid profile analysis (TG, TC, HDL, LDL, VLDL) after centrifugation at 5000 rpm for 15 minutes. Subsequently, animals were sacrificed, and the liver were excised and weighed. Liver tissues were preserved in 10% formalin for histopathological studies and processed separately to analyze oxidative stress biomarkers, including MDA, GSH, CAT, and SOD.

Measurement of Food intake and Body Weight

Daily monitoring of food intake and body weight was performed by measuring the difference between the quantity provided and the amount remaining after 24 hours for each cage. The intake was calculated in grams for food. Body weight of each rat was recorded individually on day 0 (prior to treatment initiation) and subsequently on days 7, 14, and 21 to assess the progression of Clozapine-induced weight gain and the modulatory effect of *Delonix regia* extract.

Organ Collection, Processing, and Weight Analysis

Following blood collection, rats were anesthetized, and the liver, and abdominal fat were carefully excised. The organs were washed with normal saline to remove blood residues, blotted dry, and weighed using an analytical balance. Relative organ weights were calculated and expressed as a percentage of the final body weight of each rat. Liver and kidney tissues were preserved for histopathological examination, while visceral fat was quantified to assess fat accumulation. These measurements were used to evaluate the extent of Clozapine-induced changes and the modulatory effect of *Delonix regia* extract on visceral adiposity.

Statistical Analysis

All experimental data were expressed as mean $\pm$ standard deviation (SD). Statistical comparisons among the groups were performed using one-way analysis of variance (ANOVA) followed by Tukey's post hoc test to determine intergroup significance. A p-value of less than 0.05 was considered statistically significant. Graph Pad Prism version 9.0 (GraphPad Software Inc., USA) was used to carry out all statistical analyses and graphical representations.

4.Result

Table 2: Results of Preliminary Phytochemical Investigation of *Delonix regia* Extract

Sr. No.	Phytochemical Class	Sub-test Performed	Inference
1	Alkaloids	Mayer's test	+
		Wagner's test	+
2	Flavonoids	Shinoda test	+
3	Tannins	Ferric chloride test	+
4	Saponins	Foam test	+
5	Steroids	Salkowski test	—
6	Glycosides	Keller-Kiliani test	+
7	Phenolic compounds	Ferric chloride test	+
8	Terpenoids	Salkowski test	+
9	Carbohydrates	Molisch's test	—
		Fehling's test	—
10	Proteins and Amino acids	Biuret test	—

‘+’ indicates presence; ‘—’ indicates absence in the hydroalcoholic extract of *Delonix regia*.

Effect of *Delonix regia* on Body Weight in Clozapine-treated Rats

The body weight of the animals was recorded at 3-day intervals throughout the study period. As shown in Table 4.1 and Figure 4.1, rats in the Disease Control (DC) group, which received Clozapine (5 mg/kg/day), showed a significant increase in body weight compared to the Normal Control (NC) group starting from day 9 and continuing through the end of the treatment period. Co-administration of *Delonix regia* at doses of 100 mg/kg/day (DLR1), 200mg/kg/day (DLR2), and 400 mg/kg/day (DLR3) significantly attenuated this Clozapine-induced weight gain in a dose-dependent manner. The highest dose of *Delonix regia* (400 mg/kg/day) showed the most significant reduction in body weight compared to the disease control group.

Table 3 : Effect of *Delonix regia* on body weight in Clozapine-treated female SD rats for 21 days

Days	Normal Control	Clozapine (5 mg/kg)	Clozapine + <i>Delonix regia</i> (100 mg/kg)	Clozapine + <i>Delonix regia</i> (200 mg/kg)	Clozapine + <i>Delonix regia</i> (400mg/kg)
Day 3	188.6 ± 4.21	1.90 ± 3.86	182.4 ± 3.18	191.6 ± 2.84	191.9 ± 3.08
Day 6	186.2 ± 3.43	195.3 ± 5.18	193.8 ± 3.27	172.9 ± 3.15	192.4 ± 3.19
Day 9	189.8 ± 3.57	21.6 ± 4.53*	187.5 ± 3.48#	195.2 ± 3.35#	193.1 ± 3.23##
Day 12	194.1 ± 3.76	209.8 ± 4.99**	199.3 ± 3.37#	197.1 ± 3.23##	193.8 ± 3.37##
Day 15	199.3 ± 3.92	243.5 ± 5.17**	194.7 ± 3.69#	198.6 ± 3.51##	186.5 ± 3.33##

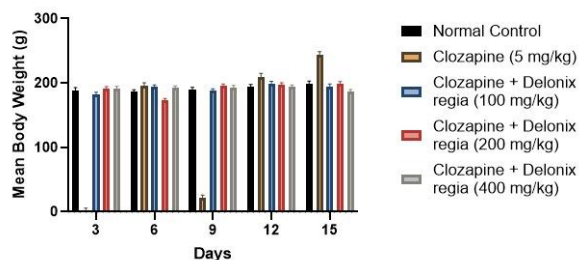


Fig no 2 :Effect of *Delonix regia* on body weight in Clozapine-treated female SD rats. Values are expressed as mean $\pm$ DLR (n=5). *p<0.05, p<0.01 vs. Normal Control group; #p<0.05, ##p<0.01 vs. Disease Control group.

Table 4: Effect of *Delonix regia* Extract on Cumulative Group-wise Mean Food Intake (g), Body Weight Gain (%) on Day 7, 14, and 21 in Clozapine-Induced Obese Rats

Group	Parameter	Day 7	Day 14	Day 21
Normal Control	Body Weight Gain	3.75 $\pm$ 0.63	6.10 $\pm$ 1.15	9.02 $\pm$ 1.08
	Food Intake	136.12 $\pm$ 5.46	252.47 $\pm$ 7.64	384.12 $\pm$ 9.01
Clozapine Control	Body Weight Gain	6.80 $\pm$ 1.25	10.29 $\pm$ 1.20	15.36 $\pm$ 1.52
	Food Intake	149.11 $\pm$ 4.10	280.02 $\pm$ 5.13	490.06 $\pm$ 7.40
DLR100 mg/kg + Clozapine	Body Weight Gain	5.25 $\pm$ 1.05	7.49 $\pm$ 0.90	11.03 $\pm$ 1.06
	Food Intake	144.20 $\pm$ 3.28	261.80 $\pm$ 5.32	396.20 $\pm$ 8.05
DLR 200 mg/kg + Clozapine	Body Weight Gain	4.53 $\pm$ 0.95	6.48 $\pm$ 0.88	9.96 $\pm$ 0.89
	Food Intake	129.75 $\pm$ 3.79	267.08 $\pm$ 6.23	397.34 $\pm$ 7.22
DLR 400 mg/kg + Clozapine	Body Weight Gain	3.90 $\pm$ 0.73	5.94 $\pm$ 0.85	8.95 $\pm$ 0.85
	Food Intake	129.32 $\pm$ 3.90	253.67 $\pm$ 6.16	385.47 $\pm$ 8.12

DLR= *Delonix regia* extract; Values are expressed as mean ± DLR (n = 5 per group).

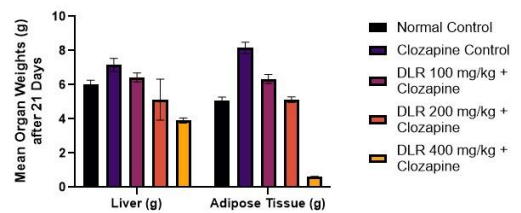


Fig no :3 Effect of *Delonix regia* on weekly food intake in Clozapine-treated female SD rats. Values are expressed as mean ± DLR (n=5). *p<0.05, p<0.01 vs. Normal Control group; #p<0.05, ##p<0.01 vs. Disease Control group.

Results of Organ Weight Analysis

Table 5: Effect of *Delonix regia* Extract on Organ Weights (g) after 21 Days

Groups	Liver (g)	Adipose Tissue (g)
Normal Control	6.04 ± 0.23	5.05 ± 0.23
Clozapine Control	7.15 ± 0.39	8.15 ± 0.34
DLR 100 mg/kg + Clozapine	6.43 ± 0.26	6.34 ± 0.26
DLR 200 mg/kg + Clozapine	5.13 ± 1.20	5.13 ± 0.16
DLR 400 mg/kg + Clozapine	3.90 ± 0.15	0.60 ± 0.04

Values are presented as mean ± DLR (n = 5).

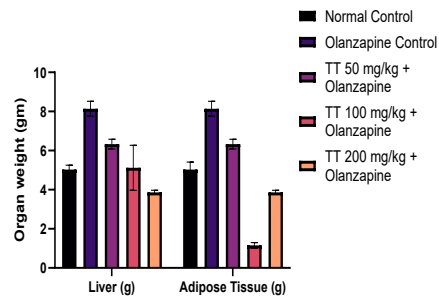


Fig no 4 :Effect of *Delonix regia* on HDL-cholesterol levels in Clozapine-treated female SD rats. Values are expressed as mean ± DLR (n=5). p<0.01 vs. Normal Control group;m#p<0.05, ##p<0.01 vs. Disease Control group.

Results of Biochemical Assays

Table 6: Oxidative Stress Markers in Liver Tissue

Groups	MDA (nmole/gm tissue)	CAT ($\mu\text{mol H}_2\text{O}_2/\text{gm tissue}$)	SOD (U/gm tissue)	GSH ($\mu\text{g/gm tissue}$)
Normal Control	38.63 ± 2.0	7.97 ± 0.10	0.36 ± 0.05	1275 ± 45.0
Clozapine Control	55.55 ± 3.9	7.75 ± 0.06	0.60 ± 0.05	824.5 ± 25.0
DLR 100 mg/kg + Clozapine	58.49 ± 3.0	7.84 ± 0.06	0.36 ± 0.07	905.5 ± 22.0
DLR 200 mg/kg + Clozapine	36.10 ± 2.1	7.96 ± 0.08	0.30 ± 0.07	947.5 ± 20.0
DLR 400 mg/kg + Clozapine	28.99 ± 1.8	7.90 ± 0.06	0.15 ± 0.06	1097 ± 25.0

Values are presented as mean $\pm$ DLR (n = 5).

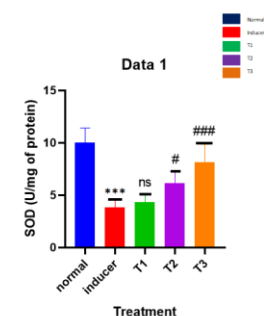


Fig no :5 Effect of *Delonix regia* on SOD activity in Clozapine-treated female SD rats. Values are expressed as mean $\pm$ DLR (n=5). $p < 0.01$ vs. Normal Control group; # $p < 0.05$, ## $p < 0.01$ vs. Disease Control group.

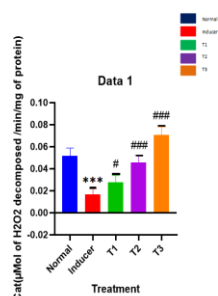


Fig no :6 Effect of *Delonix regia* on CAT activity in Clozapine-treated female SD rats. Values are expressed as mean $\pm$ DLR (n=5). $p < 0.01$ vs. Normal Control group; # $p < 0.05$, ## $p < 0.01$ vs. Disease Control group.

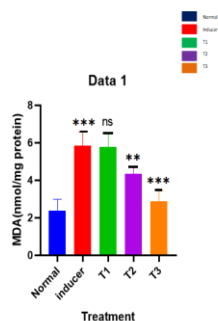


Fig no : 7 Effect of *Delonix regia* on MDA activity in Clozapine-treated female SD rats. Values are expressed as mean $\pm$ DLR (n=5). $p < 0.01$ vs. Normal Control group; # $p < 0.05$, ## $p < 0.01$ vs. Disease Control group.

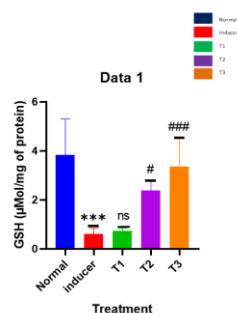


Fig no : 8 Effect of *Delonix regia* on GSH activity in Clozapine-treated female SD rats. Values are expressed as mean $\pm$ DLR (n=5). $p < 0.01$ vs. Normal Control group; # $p < 0.05$, ## $p < 0.01$ vs. Disease Control group.

Table no 7 :Results of total cholesterol, triglycerides, HDL, LDL, and VLDL

Groups	Triglycerides (mg/dl)	Cholesterol (mg/dl)	HDL (mg/dl)	LDL (mg/dl)	VLDL (mg/dl)
Normal Control	40.60 $\pm$ 1.9	46.25 $\pm$ 1.5	41.78 $\pm$ 0.5	-3.51 $\pm$ 1.2	8.11 $\pm$ 0.3
Clozapine Control	88.20 $\pm$ 3.4	62.55 $\pm$ 0.9	25.36 $\pm$ 0.9	19.55 $\pm$ 1.1	17.70 $\pm$ 0.6
DLR 100 mg/kg + Clozapine	63.15 $\pm$ 3.5	41.30 $\pm$ 0.8	36.15 $\pm$ 1.1	-6.48 $\pm$ 1.7	12.55 $\pm$ 0.8
DLR 200 mg/kg + Clozapine	50.03 $\pm$ 3.0	37.60 $\pm$ 0.7	29.67 $\pm$ 0.8	-2.02 $\pm$ 1.3	10.01 $\pm$ 0.7
DLR 400 mg/kg + Clozapine	48.40 $\pm$ 2.8	32.27 $\pm$ 1.2	28.15 $\pm$ 1.1	-5.60 $\pm$ 1.3	9.68 $\pm$ 0.5

Negative LDL values may result from formula limitations under altered triglyceride conditions.

Data are expressed as mean $\pm$ DLR (n = 5).

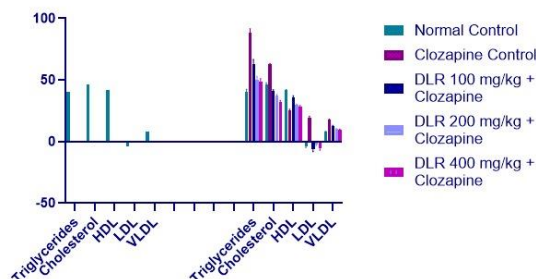


Figure :9 Effect of *Delonix regia* on HDL, LDL and VLDL level -cholesterol levels in Clozapine-treated female SD rats. Values are expressed as mean $\pm$ DLR (n=5). $p < 0.01$ vs. Normal Control group; # $p < 0.05$, ## $p < 0.01$ vs. Disease Control group.

Effect of *Delonix regia* on Histopathological Changes

Histopathological examination of Liver tissue was performed to assess the protective effect of *Delonix regia* against Clozapine-induced hepatic damage. In contrast, the Disease Control group showed significant histopathological alterations, including hepatocellular degeneration, vacuolation, fatty changes, and infiltration of inflammatory cells. Treatment with *Delonix regia* dose-dependently ameliorated these Clozapine-induced histopathological changes. The high-dose *Delonix regia* group showed the most significant improvement, with liver histology closely resembling that of the Normal Control group.

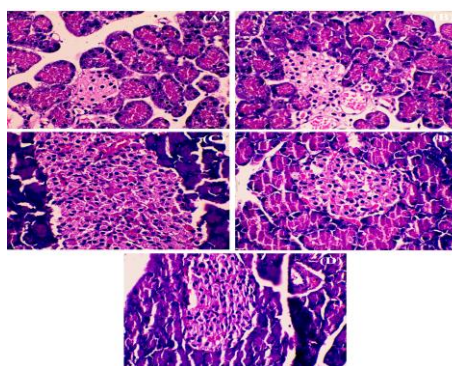


Figure:10 Photomicrographs of pancreas sections (H&E staining, 40 $\times$) from different experimental groups. (A) Normal Control: normal hepatic architecture; (B) Disease Control (Clozapine): severe hepatocellular degeneration, vacuolation, fatty changes, and inflammatory cell infiltration; (C) CLZ + DLR (100 mg/kg): moderate histopathological

changes; (D) Clozapine + DLR(200 mg/kg): mild histopathological changes; (E) Clozapine + DLR(400 mg/kg): minimal to absent histopathological changes, resembling normal pancreas architecture.

Discussion

The administration of Clozapine led to a progressive and statistically significant increase in body weight in the disease control (DC) group when compared to the normal control (NC) rats, with observable divergence beginning from day 9 and intensifying through day 21. This finding reinforces the well-established metabolic side effect of Clozapine-induced weight gain. In contrast, *Delonix regia* co-treatment significantly mitigated this weight gain in a dose-dependent manner. The highest dose of *Delonix regia* (400 mg/kg/day, DLR3) was the most effective, maintaining body weights near baseline values throughout the study. Intermediate (200 mg/kg/day, DLR2) and low doses (100 mg/kg/day, DLR1) also showed attenuation, although less pronounced. Statistical significance was evident, particularly at later time points (days 15–21), where DLR2 and DLR3 groups demonstrated highly significant reductions ($p<0.01$) compared to the DC group..

This hyperglycemic response post-glucose challenge is indicative of Clozapine-induced glucose intolerance and insulin resistance. In contrast, *Delonix regia* administration at all tested doses substantially improved glucose disposal in a dose-dependent manner. The group receiving the highest dose (400 mg/kg/day, DLR3) showed near-normal glucose values at all time points, closely approximating those of the NC group and exhibiting significant reductions compared to the DC group ($p<0.01$). The DC group retained a minimal glucose-lowering response to insulin at both 30 and 60 minutes, while the DLR3 group showed a significant increase in insulin sensitivity ($p<0.01$ vs. DC), with blood glucose reductions closely paralleling the NC group. Collectively, these results confirm *Delonix regia* efficacy in counteracting Clozapine induced glucose dysregulation by enhancing both glucose tolerance and insulin sensitivity.

The lipid profile analysis at the end of the treatment period demonstrated that Clozapine administration resulted in marked dyslipidemia in the disease control (DC) group, characterized by significant elevations in total cholesterol (TC), triglycerides (TG), low-density lipoprotein (LDL), and very low-density lipoprotein (VLDL), along with a concomitant reduction in high-density lipoprotein (HDL) compared to the normal control (NC) group (Table 8.6; Figures 8.6–8.10). These findings confirm the adverse metabolic effects of chronic Clozapine use, which

mirrors clinical observations in antipsychotic-associated metabolic syndrome. The administration of *Delonix regia* to a statistically significant and dose-dependent improvement in all lipid parameters. Even at the lowest dose (100 mg/kg/day, DLR1), *Delonix regia* significantly reduced TC, TG, LDL, and VLDL levels ($p < 0.05$) while increasing HDL. These improvements became more prominent with the intermediate (DLR2) and high doses (DLR3), with DLR3 producing values nearly indistinguishable from the NC group ($p < 0.01$ vs. DC group across all parameters). The most pronounced effect was observed in the DLR3 group (400 mg/kg/day), where total cholesterol and triglyceride levels were reduced to 90.62 ± 8.17 mg/dL and 83.41 ± 7.68 mg/dL respectively—values much closer to the NC group. Similarly, LDL and VLDL levels were normalized, and HDL levels were significantly elevated, reaching 40.85 ± 3.81 mg/dL, nearly matching normal physiological values. These observations suggest that *Delonix regia* exerts potent lipid-modulating effects in addition to its glycemic benefits. *Delonix regia* treatment markedly reduced HbA1c in a dose-dependent manner, with the high-dose group (DLR3, 400 mg/kg/day) demonstrating values ($5.68 \pm 0.49\%$) comparable to those of the NC group ($5.43 \pm 0.48\%$). The intermediate (DLR2) and low doses (DLR1) also achieved significant reductions ($p < 0.01$ and $p < 0.05$, respectively), supporting *Delonix regia* effectiveness in restoring long-term glycemic control.

The assessment of organ weights revealed that Clozapine treatment significantly increased the weights of vital organs such as the pancreas, kidney, heart, pancreas, and adipose tissue, while paradoxically reducing total fat content, reflecting systemic metabolic dysregulation and possible organ hypertrophy. Histological evaluation further substantiated the biochemical and anatomical findings. Pancreas sections from the DC group showed pronounced hepatocellular degeneration, fatty changes, vacuolation, and infiltration of inflammatory cells, confirming hepatotoxic effects of chronic administration. *Delonix regia* treatment significantly reduced sleeping time in a dose-dependent fashion, with the DLR3 group (52.87 ± 4.76 min) closely approximating NC levels (48.35 ± 4.37 min).

Conclusion

The pharmacological evaluation of *Delonix regia* extract demonstrated a significant protective effect against Clozapine-induced body weight gain and dyslipidemia in female Sprague-Dawley rats. Treatment with the extract resulted in a notable reduction in body weight, total cholesterol, triglycerides, LDL levels, and an increase in HDL levels compared to the clozapine-only group. These findings suggest that *Delonix regia* possesses anti-obesity and lipid-lowering properties, possibly due to its phytoconstituents such as saponins, flavonoids, and alkaloids, which may modulate lipid metabolism and energy balance. Further clinical investigations are recommended to confirm its therapeutic potential in managing antipsychotic-induced metabolic disturbances.

Reference :

1. Jameel Ahmed¹, S.A.Nirmal^{*1}, R.A.Rub², S.K.Budhavale³ and S.R. Pattan,^{AN} OVERVIEW OF *DELONIX REGIA*: CHEMISTRY AND PHARMACOLOGICAL PROFILE, Pharmacologyonline 2: 544-549 (2009)
2. Satish S, Mohana DC, Raghavendra MP, Raveesha KA. Antifungal activity of some plant extracts against important seed borne pathogens of aspergillus sp. J. Agri. Techn., 2007; 3(1): 109-119.
3. Trease GE, Evans WC. Trease and Evans Pharmacognosy. 15th ed. Singapore: Harcourt Brace and Company Asia Pvt. Ltd; 2002. A taxonomic approach to the study of medicinal plants and animal derived drugs; p. 27.
4. Duke J, Duke PK, Cellier JL. 2nd edn. United States: CRC Press; 2002. Duke Handbook of medicinal herbs; p. 595.
5. Nadkarni KM. Mumbai: Popular Prakashan; 1927. Indian Materia Medica; pp. 1230–1.
6. Mohammed Hosny, Ehab A. Ragab, Hamdoon A. Mohammed and Mohammed F. Abd Elwahab, PHYTOCONSTITUENTS FROM *DELONIX REGIA* RAF ROOTS AND THEIR BIOLOGICAL ACTIVITIES, Az. J. Pharm Sci. Vol. 46, September, 2012.
7. Baderschneider, B., Winterhalter, P. (2001): "Isolation and characterization of novel benzoates, cinnamates, flavonoids, and lignans from Riesling wine and screening for antioxidant activity" J. Agr. Food Chem. 49, 2788-2798.
8. P. Dixit a, Shivkumar S. Sammeta a, Mrunali D. Dhokne a, Shubhada Mangrulkar a, Manoj A. Upadhya b, Milind J. Umekar a, Brijesh G. Taksande a, Nandkishor R. Kotagale ,Chronic

agmatine treatment prevents olanzapine-induced obesity and metabolic dysregulation in female rats, *Brain Research Bulletin*, Volume 191, December 2022, Pages 69-77.

9. Behdani F, Roudbaraki SN, Saberi-Karimian M, Tayefi M, Hebrani P, Akhavanrezayat A, Amlashi SV, Ferns GA, Ghayour-Mobarhan M (2018) Assessment of the efficacy of omega-3 fatty acids on metabolic and inflammatory parameters in patients with schizophrenia taking clozapine and sodium valproate. *Psychiatry Res* 261:243–247 S0165-1781(16)31314-2.

10. Elias Wagner^{1,✉,#}, Spyridon Siafis^{2,#}, Piyumi Fernando³, Peter Falkai¹, William G Honer⁴, Astrid Röhl³, Dan Siskind^{5,6}, Stefan Leucht², Alkomiet Hasan, Efficacy and safety of clozapine in psychotic disorders—a systematic quantitative meta-review, 2021 Sep 22;11:487. doi: [10.1038/s41398-021-01613-2](https://doi.org/10.1038/s41398-021-01613-2).

11. Vance L. Albaugh, Cathy R. Henry, Nicholas T. Bello, Andras Hajnal, Susan L. Lynch, Beth Halle, Christopher J. Lync, Hormonal and Metabolic Effects of Olanzapine and Clozapine Related to Body Weight in Rodents. <https://doi.org/10.1038/oby.2006.6>.

12. Kane J, Honigfeld G, Singer J, Meltzer H. Clozapine for the treatment-resistant schizophrenic. A double-blind comparison with chlorpromazine. *Arch Gen psychiatry*. 1988;45:789–96. doi: [10.1001/archpsyc.1988.01800330013001](https://doi.org/10.1001/archpsyc.1988.01800330013001).

13. Syed Shoib Md Hussaini, Akram A Naikwadi, Narsapur VU, ROLE OF METFORMIN ON CLOZAPINE INDUCED DYSLIPIDAEMIA IN WISTAR RATS, *International Journal of Current Research in Physiology and Pharmacology (IJCRPP)* 10.31878/ijcrpp.2018.21.1.

14. Luiza Ferracini Cunha¹, Mariana Aubin Ongaratto², Marcelo Endres², Alethea Gatto Barschak¹ Modelling hypercholesterolaemia in rats using high cholesterol diet, 2021 Mar 12;102(2):74–79. doi: [10.1111/iep.12387](https://doi.org/10.1111/iep.12387).

15. Pearl Pinto¹, Sivaprakasam Chinnarasu², Mohanraj Sadasivam³, Louis Cojandaraj¹, Conceivable Mechanisms of Clozapine Propagated Dyslipidemia- A Short Review, *Research & Reviews: Journal of Pharmaceutical Analysis* e-ISSN: 2320-0812.

16. Howes OD, et al. Treatment Resistant Schizophrenia: Treatment Response and Resistance in Psychosis (TRRIP) Working Group Consensus Guidelines on Diagnosis and Terminology. *Am J Psychiatry*. 2017;174:216–229.

17. Honer W, Thornton A, Sherwood M, MacEwan G, Ehmann T, Williams R et al. Conceptual and methodological issues in the design of clinical trials of antipsychotics for the treatment of Schizophrenia. *CNS Drugs*. 2007;21(9):699-714.

18. Rummel-Kluge C, Komossa K, Schwarz S, Hunger H, Schmid F, Kissling W et al. Second-generation antipsychotic drugs and extrapyramidal side effects: a systematic review and meta-analysis of head-to-head comparisons. *Schizophrenia Bulletin*. 2010;38(1):167-177.
19. Rajesh Asija, Charanjeet Singh, Hemlata, A Comprehensive Review on Antihyperlipidemic Activity of Various Medicinal Plants, *International Journal of Current Pharmaceutical Review and Research*; 7(6); 407-415.
20. Abrams P, Andersson KE, Buccafusco JJ, et al. (2006) Muscarinic receptors: their distribution and function in body systems, and the implications for treating overactive bladder. *Br J Pharmacol* 148: 565–578.
21. Paul D Morrison^{1,2,✉}, Sameer Jauhar^{2,3}, Allan H Young, The mechanism of action of clozapine, 2025 Feb 13;39(4):297–300. doi: [10.1177/02698811251319458](https://doi.org/10.1177/02698811251319458).
22. Jacobi I Cunningham, David J Eyerman, Mark S Todtenkopf, Reginald L Dean, Daniel R Deaver, Connie Sanchez and Mark Namchuk, Samidorphan mitigates olanzapine-induced weight gain and metabolic dysfunction in rats and non-human primates, *Journal of Psychopharmacology* 2019, Vol. 33(10) 1303–1316 © The Author(s) 2019.
23. Ader M, Kim SP, Catalano KJ, et al. (2005) Metabolic dysregulation with atypical antipsychotics occurs in the absence of underlying disease: A placebo-controlled study of olanzapine and risperidone in dogs. *Diabetes* 54: 862–871.
24. Albaugh VL, Judson JG, She P, et al. (2011) Olanzapine promotes fat accumulation in male rats by decreasing physical activity, repartitioning energy and increasing adipose tissue lipogenesis while impairing lipolysis. *Mol Psychiatry* 16: 569–581.
25. Czyzyk TA, Romero-Pico A, Pintar J, et al. (2012) Mice lacking delta opioid receptors resist the development of diet-induced obesity. *FASEB J* 26: 3483–3492.
26. De Hert M, Detraux J, van Winkel R, et al. (2011b) Metabolic and cardiovascular adverse effects associated with antipsychotic drugs. *Nat Rev Endocrinol* 8: 114–126.
27. Freedman R (2003) Schizophrenia. *N Engl J Med* 349: 1738–1749. Gallagher CJ, Gordon CJ, Langefeld CD, et al. (2006) Association of the mu-opioid receptor gene with type 2 diabetes mellitus in an African American population. *Mol Genet Metab* 87: 54–60.
28. Jain S, Bhargava M and Gautam S (2006) Weight gain with olanzapine: Drug, gender or age? *Indian J Psychiatry* 48: 39–42.

- 29.Kapur S, Zipursky RB and Remington G (1999) Clinical and theoretical implications of 5-HT₂ and D₂ receptor occupancy of clozapine, risperidone, and olanzapine in schizophrenia. *Am J Psychiatry* 156: 286–293.
- 30.Wenyi Zhu, Yijie Du, Hong Meng, Yinmao Dong, and Li Li . A review of traditional pharmacological uses, phytochemistry, and pharmacological activities of *Delonix regia* *Chemistry Central Journal*,(2017) 11(1). <https://doi.org/10.1186/s13065-017-0289-x>
- Ivanka B.
- 31.Semerdjieva and Valtcho D. Zheljazkov. Chemical Constituents, Biological Properties, and Uses of *Tribulus terrestris*: A Review. *Natural Product Communications*,(2019) 14(8), 1934578X1986839. <https://doi.org/10.1177/1934578x19868394>
- 32.Svensson, Camilla K.; Larsen, Julie R.; Vedtofte, Louise; Jakobsen, Mathilde S. L.; Jespersen, Hans R.; Jakobsen, Michelle I.; Koyuncu, Kamuran; Schjerning, Ole; Nielsen, Jimmi; Ekstrøm, Claus T.; Correll, Christoph U.; Vilsbøll, Tina; Fink-Jensen, Anders (2018). One-Year Follow-up on Liraglutide Treatment for Prediabetes and Overweight/Obesity in Clozapine- or Olanzapine-Treated Patients. *Acta Psychiatrica Scandinavica*, (), –. doi:10.1111/acps.12982
33. Lin CH, Lin SC, Huang YH, Wang FC, Huang CJ. Early prediction of olanzapine-induced weight gain for schizophrenia patients. *Psychiatry Res.* 2018 May;263:207-211. doi: 10.1016/j.psychres.2018.02.058. Epub 2018 Mar 30. PMID: 29574355.1
34. Hardy TA, Henry RR, Forrester TD, Kryzhanovskaya LA, Campbell GM, Marks DM, Mudaliar S. Impact of olanzapine or risperidone treatment on insulin sensitivity in schizophrenia or schizoaffective disorder. *Diabetes Obes Metab.* 2011 Aug;13(8):726-35. doi: 10.1111/j.1463-1326.2011.01398.x. PMID: 21435142.
- 35.Lanktree, Matthew B. (2018). Genomic and Precision Medicine || Metabolic Syndrome. , (), 47–63. doi:10.1016/B978-0-12-801812-5.00015-9.
36. Huhn M, Nikolakopoulou A, Schneider-Thoma J, Krause M, Samara M, Peter N, Arndt T, Bäckers L, Rothe P, Cipriani A, Davis J, Salanti G, Leucht S. Comparative efficacy and tolerability of 32 oral antipsychotics for the acute treatment of adults with multi-episode schizophrenia: a systematic review and network meta-analysis. *Lancet.* 2019 Sep 14;394(10202):939-951. doi: 10.1016/S0140-6736(19)31135-3. Epub 2019 Jul 11. Erratum in: *Lancet.* 2019 Sep 14;394(10202):918. PMID: 31303314; PMCID: PMC6891890 .

37. tomova, m., r. Gjulemetova, s. Zarkova, et al. 1981. Steroidal saponins from tribulus terrestris l. With a stimulating action on the sexual functions. In international conference of chemistry and biotechnology of biologically active natural products, varna, bulgaria. September 21–26, 3: 298
38. MINGJUAN, L., Q. WEIJING, W. YIFEI, et al. 2002. Hypoglycemic effect of saponin from Tribulus terrestris. J. Chinese Med. Mat. 25: 420–422.
39. Yousra Abdel-Mottaleb", Howaida S. Ali, Mohamed K. El-Kherbetawy, Amany Y. Elkazzaz, Mohamed H. ElSayed, Amr Elshormilisy, Saponin-rich extract of Tribulus terrestris alleviates systemic inflammation and insulin resistance in dietary obese female rats: Impact on adipokine/hormonal disturbances (2022) <https://doi.org/10.1016/j.biopha.2022.112639>.
40. Ching-Hua Lina,b , Shih-Chi Lina , Yu-Hui Huang , Fu-Chiang Wang , Chun-Jen Huang Early prediction of olanzapine-induced weight gain for schizophrenia patients (2018) <https://doi.org/10.1016/j.psychres.2018.02.058>.
41. K.V. Sailaja, V. Leela Shivaranjani, H. Poornima, S.B.Md. Rahamathulla, K. Lakshmi Devi PROTECTIVE EFFECT OF TRIBULUS TERRESTRIS L. FRUIT AQUEOUS EXTRACT ON LIPID PROFILE AND OXIDATIVE STRESS IN ISOPROTERENOL INDUCED MYOCARDIAL NECROSIS IN MALE ALBINOWISTAR RATS .(2013)
42. Agnieszka Kolasa 1 , Paweł Szumilas 3 , Ewa Stachowska 2 and Barbara Wiszniewska 1 The Obscure Effect of Tribulus terrestris Saponins Plus Inulin on Liver Morphology, Liver Fatty Acids, Plasma Glucose, and Lipid Profile in SD Rats with and without Induced Type 2 Diabetes Mellitus(2021) . <https://doi.org/10.3390/ijms22168680>
43. Mrityunjaya B. Ullagaddi, B. M. Patil, and Pukar Khanal , Beneficial effect of Zingiber officinale on olanzapine-induced weight gain and metabolic changes Published online 2021 Jan
44. Eagappan, K.; Sasikumar, S.; Brindha, D. Antioxidant capacity insolvent and cooked extracts of Tribulus Terrestris L Fruit. Int. J. Biol. Pharm. Res. 2015, 6, 63–67.
45. Kumar R, Patel DK, Prasad SK, Sairam K, Hemalatha S. Antidiabetic activity of alcoholic root extract of Caesalpinia digyna in streptozotocin-nicotinamide induced diabetic rats. Asian Pac J Trop Biomed. 2012;2(2):934-40. Doi: 10.1016/S2221-1691(12)60340-2.
46. Jyoti Kaushik¹, Simran Tandon², Rishi Bhardwaj ³, Tanzeer Kaur³, Surinder Kumar Singla⁴, Jitender Kumar¹ & Chanderdeep Tandon¹, Delving into the Antiurolithiatic Potential of Tribulus terrestris Extract Through –In Vivo Efficacy and Preclinical Safety Investigations in Wistar Rats(2019) <https://doi.org/10.1038/s41598-019-52398-w>