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Original Article

Modulating Metabolic and Cardiovascular Adverse Effects of Olanzapine with *Theobroma cocoa* a Preclinical Insight into Synergistic Cardioprotection

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ABSTRACT

Background: Olanzapine, a widely prescribed atypical antipsychotic, is associated with significant cardiometabolic side effects, including hypertension, dyslipidaemia, oxidative stress, inflammation, and QT interval prolongation. Natural substances possessing antioxidant and anti-inflammatory characteristics, like *Theobroma cocoa* which is abundant in polyphenols, could provide a promising therapeutic approach to alleviate these negative effects. **Objectives:** To investigate the cardiovascular and metabolic impact of Olanzapine, cocoa, and their combination in a controlled experimental model, focusing on blood pressure, lipid profile, inflammatory and oxidative stress markers, weight gain, and QT interval alterations. **Materials and Methods:** Male Wistar rats were categorized into control, Olanzapine (5 mg/kg/day), OLZ+TCE (50 mg/kg/day), OLZ+TCE (100 mg/kg/day), OLZ+TCE (200 mg/kg/day) and combination groups for an 8-week treatment period. Systolic blood pressure was evaluated via the tail-cuff method. Serum concentration of LDL, HDL, triglycerides, C-reactive protein (CRP) and malondialdehyde (MDA) were analyzed. Body weight and electrocardiographic QT interval were also assessed. Data were subjected to analysis using one-way ANOVA followed by Tukey's post hoc test ($p < 0.05$). **Results:** Olanzapine substantial increased systolic blood pressure, LDL, triglycerides, CRP, MDA levels, QT interval, and body weight, while reducing HDL cholesterol ($p < 0.05$ to $p < 0.001$ vs. control). TCE+OLZ (100,200 mg/kg+5mg/kg) demonstrated cardio protective properties by enhancing all assessed parameters. Co-administration of cocoa with Olanzapine attenuated most Olanzapine-induced changes, though QT interval prolongation was not significantly reversed. **Conclusion:** *Theobroma cocoa* demonstrates potential in mitigating several cardio metabolic side effects of Olanzapine in a preclinical model. These findings support further exploration of cocoa polyphenols as adjunctive agents in antipsychotic therapy to enhance cardiovascular safety.

Keywords: Olanzapine, Cocoa, Cardiovascular, Oxidative Stress, CRP, Lipid Profile, QT Interval, Metabolic Syndrome.

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INTRODUCTION

Olanzapine is a commonly utilized atypical antipsychotic medication, mainly indicated for the treatment of schizophrenia and bipolar affective disorders. Although its effectiveness in controlling symptoms is thoroughly established, its administration is often associated with significant metabolic adverse effects, such as weight gain, changes in lipid metabolism, insulin resistance, and heightened cardiovascular risk (Pillinger *et al.*, 2020; Reynolds & Kirk, 2010). These adverse effects are critical contributors to decreased medication adherence and elevated morbidity among patients receiving long-term therapy (Correll *et al.*, 2015).

The metabolic disturbances associated with olanzapine are thought to result from its interaction with neurotransmitter receptors that influence appetite regulation, insulin action, and lipid storage. For instance, antagonism of histamine H1 and serotonin 5-HT2C receptors is associated with heightened appetite and increased adiposity, whereas disruption of muscarinic and adrenergic pathways may negatively impact glucose and lipid homeostasis (Teff *et al.*, 2013; Albaugh *et al.*, 2011).

Given these challenges, interest has grown in identifying natural compounds that can counteract these adverse outcomes. One such candidate is *Theobroma cocoa*, the source of cocoa, known for its high concentration of bioactive flavonoids and

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methylxanthines. These phytochemicals have demonstrated promising cardiovascular and metabolic benefits, including improvement in endothelial function, a decrease in oxidative stress, and an improvement in insulin sensitivity (Shrime *et al.*, 2011; Mellor *et al.*, 2013).

This research examines the safeguarding properties of *Theobroma cocoa* against olanzapine-induced cardio metabolic alterations in a preclinical model. The primary objective is to evaluate whether co-administration of cacao extract can mitigate the metabolic and cardiovascular toxicity commonly observed with olanzapine treatment, thereby supporting its potential as an adjunctive therapeutic approach.

MATERIALS AND METHODS

Animals

Male Wistar rats weighing between (200-250 g) were sourced from the Central Animal Research Facility. They were maintained in standard laboratory conditions featuring a 12-hr light/dark cycle and were provided with unrestricted access to standard rodent chow and water. The experimental procedures received approved from the Institutional Animal Ethical Committee (IAEC) of pharmacology-II Laboratory at Pravara Rural College of Pharmacy, Pravaranagar. The CPCSEA Registration No 1942/P0/Re/S/17/CPCSEA/2023/01/05/01. Prior to the commencement of the study the animals were acclimatized under a 12-hr light/dark cycle for a duration of 7 days before the study.

Chemicals

Olanzapine was acquired from Yarrow Chem products located in Mumbai, India. The Olanzapine was then dissolved in 0.1 N hydrochloric acid, and pH was modified to -5.5 (using 0.1 N NaOH) and final volume being adjusted using distilled water (Parasuraman, *et al* 2017).

Collection and preparation of extraction of *Theobroma cocoa* (TCE)

Cocoa seeds was acquired from VALLEYSPICE- specifically Cocoa beans sourced from Idukki District in Kerala, India for the purpose of extraction. The collected pods were meticulously washed under running water, chopped, shade dried, and processed into coarse power using a pulverizer. The powder was then defatted with petroleum ether (bp 40-60 °C) and subjected to maceration (80% ethanol) within a sealed container for a week. Following this the mixture was filtered, concentrated, lyophilized, and stored in an appropriate container for further use (Patil, *et al* 2022).

Experimental Groups

The rats were assigned to five groups at random (n = 8 per group):

Control: Received vehicle (saline).

Olanzapine (OLZ): Administered Olanzapine (5 mg/kg/day) orally.

Olanzapine + TCE 50 mg/kg: Received Received Administered both Olanzapine and *Theobroma cocoa* extract (50 mg/kg/day) orally.

Olanzapine + TCE 100 mg/kg: Received Administered both Olanzapine and *Theobroma cocoa* extract (100 mg/kg/day) orally.

Olanzapine + TCE 200 mg/kg: Received Administered both Olanzapine and *Theobroma cocoa* extract (200 mg/kg/day) orally.

Treatment Duration

The treatment lasted for 8 weeks, with daily administration of respective treatments.

Assessment Parameters

Blood Pressure Monitoring: Tail-Cuff Technique

Systolic Blood Pressure (SBP) was assessed through a non-invasive tail-cuff technique in awake rats. The procedure involved placing an inflatable cuff around the tail, which detects the occlusion and resumption of blood flow to determine systolic values. Proper habituation of animals and control of ambient temperature are essential to minimize stress-induced variability and obtain reliable data (Kurtz *et al.*, 2005; Feng *et al.*, 2008).

Serum Lipid Profile Estimation

The serum concentrations of Low-Density Lipoprotein (LDL), High-Density Lipoprotein (HDL), and triglycerides were determined utilizing enzymatic colorimetric assay kits. These standardized kits are based on enzymatic hydrolysis followed by spectrophotometric detection and are widely used for lipid profiling due to their sensitivity and reproducibility (Allain *et al.*, 1974).

Inflammatory Marker Assessment: CRP via ELISA

C-reactive protein (CRP), recognised as a sensitive biomarker of systemic inflammation, was measured utilizing a high-sensitivity ELISA kit. This technique allows detection of low-level inflammatory changes with high specificity and is routinely employed in cardiovascular and metabolic research (Rifai & Ridker, 2001).

Oxidative Stress Marker: MDA via TBARS Assay

Malondialdehyde (MDA), a significant byproduct of lipid peroxidation, was evaluated through the thiobarbituric acid reactive substances (TBARS) assay. The MDA-TBA complex generate a pink chromogen that can be quantified at 532 nm making it a dependable markersfor assessing oxidative stress levels in both tissue and serum samples (Ohkawa *et al.*, 1979).

Body Weight Monitoring

Body weight was recorded weekly using a precision electronic balance. This serves as an essential indicator of systemic toxicity, metabolic changes, and overall animal health during pharmacological interventions (OECD, 2001).

Electrocardiographic (ECG) and QT Interval Analysis

Electrocardiograms (ECGs) were recorded under light anesthesia using standard lead II configuration to evaluate cardiac electrical function, including QT intervals. The QT interval, adjusted for heart rate, indicates the duration of ventricular depolarization and repolarization. Anesthetic effects on ECG readings were controlled to minimize variability (Mitchell *et al.*, 1998; Sarma *et al.*, 1990).

Statistical Analysis

Data are presented as the Mean ± with Standard Deviation (SD). Statistical analysis was conducted using one-way ANOVA followed by Tukey's *post hoc* test. A *p*-value of < 0.05 was deemed statistically significant.

RESULTS

Systolic Blood Pressure (SBP)

The administration of olanzapine resulted in a notable elevation in systolic blood pressure recorded at (132 ± 6 mmHg, $p < 0.01$) in contrast to the control group (118 ± 5 mmHg). Co-treatment with *Theobroma cocoa* extract (TCE) at 50, 100, and 200 mg/kg doses progressively reduced SBP to 128 ± 5 mmHg ($p < 0.05$), 123 ± 4 mmHg ($p < 0.01$), and 120 ± 4 mmHg ($p < 0.01$ respectively, indicating dose-dependent attenuation of olanzapine-induced hypertension (Figure 1).

Lipid Profile

Olanzapine significantly elevated LDL cholesterol (145 ± 12 mg/dL, $p < 0.001$) and triglycerides (185 ± 15 mg/dL, $p < 0.001$), while reducing HDL cholesterol (44 ± 5 mg/dL, $p < 0.05$) compared to controls. The co-treatment with TCE resulted in a dose-dependent enhancement of the lipid profile characterized by a reduction in LDL and triglycerides levels alongside a restoration of HDL levels. The highest dose (200 mg/kg) brought LDL and triglycerides close to control values and significantly increased HDL (52 ± 4 mg/dL, $p < 0.01$) (Table 1).

C - reactive protein (CRP)

Olanzapine markedly raised CRP levels (5.2 ± 0.6 mg/L, $p < 0.001$) relative to controls (2.5 ± 0.3 mg/L). The co-treatment with TCE lead to a significant reduction in CRP level in a dose-dependent manner, particularly at the dosage of 200 mg/kg dose lowering CRP to 2.8 ± 0.3 mg/L ($p < 0.01$ vs. olanzapine alone) (Figure 2).

Oxidative Stress (MDA)

MDA levels increased significantly after olanzapine treatment (3.9 ± 0.3 µmol/L, $p < 0.001$) versus control (2.1 ± 0.2 µmol/L). Co-administration of TCE decreased MDA levels dose-dependently, with the 200 mg/kg dose nearly normalizing oxidative stress (2.4 ± 0.2 µmol/L, $p < 0.01$ vs. olanzapine) (Figure 3).

Body Weight Gain

Olanzapine caused significant weight gain (4.6 ± 0.4 kg, $p < 0.001$) compared to controls (0.8 ± 0.2 kg). TCE co-treatment significantly decreased weight gain in a dose-dependent manner,

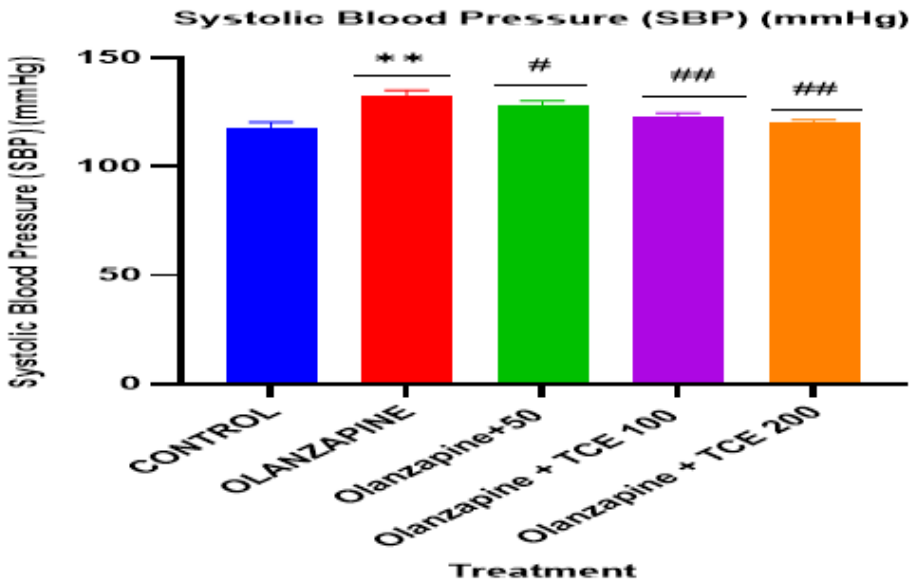

Figure 1: Systolic blood pressure (mm/hg) in rats treated with vehicle olanzapine (2 mg/kg/day), OLZ plus TCE (50, 100,200 mg/kg/day). ** p <0.01 compared to normal, # p <0.05, ## p <0.001 compared to Olanzapine.

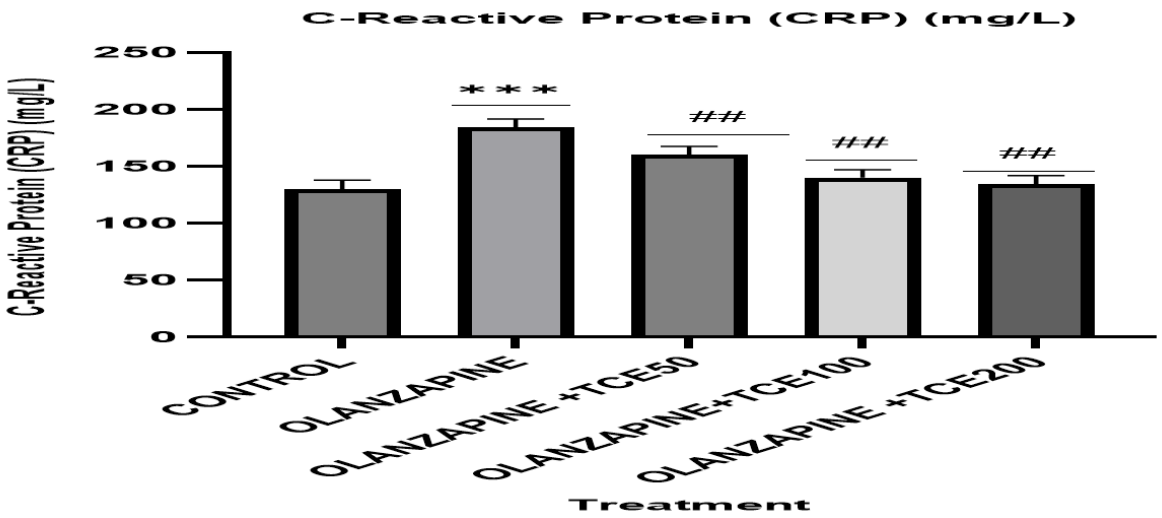

Figure 2: C- Reactive Protein (CRP) (mg/L) in rats treated with vehicle olanzapine (2 mg/kg/day), OLZ plus TCE (50, 100,200 mg/kg/day). *** p <0.001 compared to normal, ## p <0.001 compared to Olanzapine

Table 1: **Lipid Profile.**

Group	LDL (mg/dL) Mean±SEM	HDL (mg/dL) Mean±SEM	Triglycerides (mg/dL) Mean±SEM
Control	100±10	52±4	130±12
Olanzapine	145±12 ***	44±5 *	185±15 ***
Olanzapine+TCE 50	135±11 ##	47±5 #	160±13 ##
Olanzapine+TCE 100	120±10 ##	50±5 ##	140±12 ##
Olanzapine+TCE 200	110±9 ##	52±4 ##	135±11 ##

* $p < 0.05$, *** $p < 0.001$ vs Control; # $p < 0.05$, ## $p < 0.01$ vs Olanzapine

with the maximum dosage restricting weight gain to 2.2 ± 0.2 kg ($p < 0.01$ vs. olanzapine) (Table 2).

QT Interval

Olanzapine significantly prolonged the QT interval (455 ± 15 Ms, $p < 0.01$ vs. control). Cocoa extract co-treatment slightly decreased QT prolongation but not significantly, with values remaining above control levels (440 ± 12 Ms at 200 mg/kg) (Table 3).

DISCUSSION

Olanzapine is well-known for its effectiveness in treating psychiatric condition; nevertheless, its prolonged use is frequently constrained by considerable cardiometabolic adverse effects. In alignment with previous studies, our findings confirm that olanzapine elevates systolic blood pressure, increases serum LDL and triglyceride levels, induces oxidative stress (MDA), raises inflammation markers (CRP), prolongs the QT interval, and promotes significant weight gain (Pillinger *et al.*, 2020; Reynolds & Kirk, 2010). These effects are largely attributed to olanzapine's antagonism of receptors such as histamine H1, serotonin 5-HT2C, and muscarinic receptors, which regulate appetite, lipid storage, and glucose metabolism (Teff *et al.*, 2013; Albaugh *et al.*, 2011).

Table 2: **Body Weight Gain (kg).**

Group	Weight Gain (kg) Mean±SEM
Control	0.8±0.2
Olanzapine	4.6±0.4 ***
Olanzapine + TCE 50	3.5±0.3 ##
Olanzapine + TCE 100	2.8±0.3 ##
Olanzapine + TCE 200	2.2±0.2 ##

*** $p < 0.001$ vs Control; ## $p < 0.01$ vs Olanzapine

A notable finding of this study is the cardioprotective effect observed with *Theobroma cocoa* extract (TCE) co-treatment, particularly at higher doses. Cocoa's rich polyphenolic content-primarily flavonoids such as epicatechin-has been linked to improvements in endothelial function, nitric oxide synthesis, and vascular tone, which may explain the observed dose-dependent reduction in systolic blood pressure (Grassi *et al.*, 2005; Shrime *et al.*, 2011).

In terms of lipid regulation, olanzapine-induced dyslipidemia was effectively countered by cocoa extract. Prior research has demonstrated that cocoa polyphenols diminish the LDL oxidation and modulate hepatic lipid metabolism, thereby improving lipid

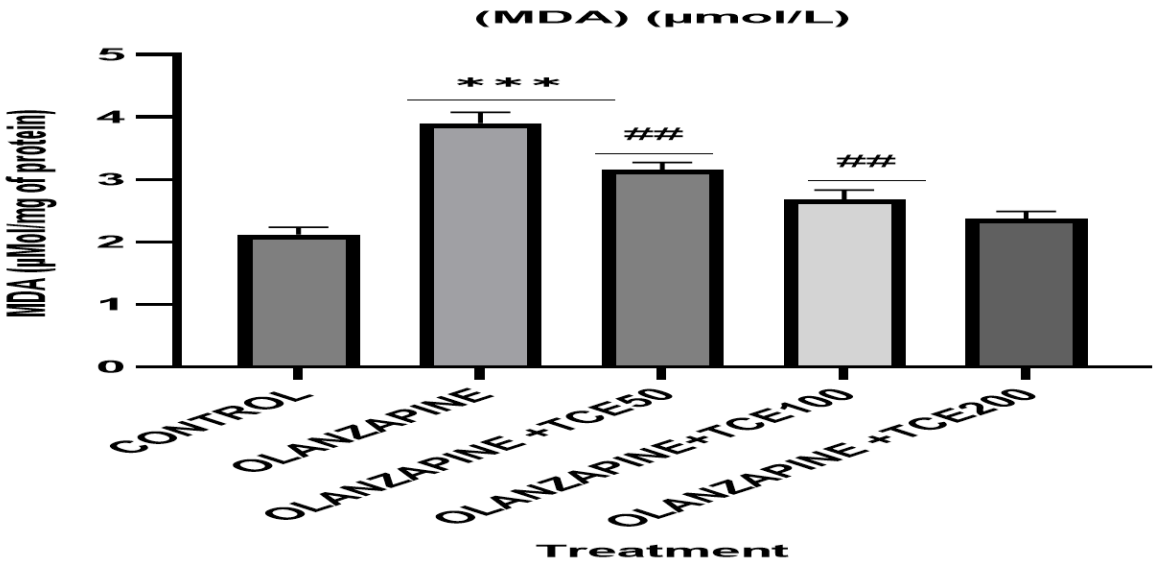

Figure 3: MDA (Micro mol/L) in rats treated with vehicle olanzapine (2 mg/kg/day), OLZ plus TCE (50, 100,200 mg/kg/day). *** p <0.001 compared to normal, ## p <0.001 compared to Olanzapine.

Table 3: **QT Interval (ms).**

Group	QT Interval (ms) Mean±SEM
Control	410±10
Olanzapine	455±15 **
Olanzapine + TCE 50	450±14
Olanzapine + TCE 100	445±13
Olanzapine + TCE 200	440±12

** p < 0.01 vs Control; no significant difference vs Olanzapine for co-treated groups.

profiles (Mellor *et al.*, 2013). The increase in HDL levels and normalization of LDL and triglycerides in the cocoa-treated groups support these cardiometabolic benefits.

Oxidative stress and inflammation are critical pathways in cardiovascular disease, and our study corroborates earlier findings that olanzapine increases both (da Silva Dias *et al.*, 2014). Cocoa's antioxidant effects, driven by its flavonoids, effectively lowered MDA and CRP levels, indicating reduced lipid peroxidation and systemic inflammation (Katz *et al.*, 2011; Rifai & Ridker, 2001).

Weight gain-a well-documented side effect of olanzapine-was significantly reduced in animals co-treated with cocoa. This phenomenon may entail the activation of AMP-activated protein kinase (AMPK) and improved energy metabolism, consistent with the mechanisms proposed in prior preclinical studies (Nogueira *et al.*, 2011).

However, cocoa co-treatment had only a modest effect on QT interval prolongation, which remained statistically non-significant. Since QT prolongation is often linked to direct inhibition of cardiac potassium channels (e.g., hERG), cocoa's mechanism of action may not adequately target these electrophysiological disruptions (Vieweg *et al.*, 2009).

In conclusion, this research underscores the potential of *Theobroma cocoa* as an adjunctive therapy to alleviate several olanzapine-induced cardiovascular and metabolic disturbances, though further work is needed to understand its limited effects on cardiac electrical activity.

CONCLUSION

This study demonstrates that *Theobroma cocoa* extract significantly mitigates several cardio metabolic side effects induced by olanzapine, including hypertension, dyslipidaemia, oxidative stress, inflammation, and excessive weight gain in a dose-dependent manner. While cocoa improved most parameters, it had limited effect on olanzapine-induced QT interval prolongation. These findings highlight the potential of cocoa polyphenols as a supportive adjunct therapy to enhance cardiovascular safety during antipsychotic treatment.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

ABBREVIATIONS

TCE: *Theobroma cocoa* 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.

ETHICAL STATEMENTS

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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