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Appraisal of TGR-5 Ligand Ciprofloxacin in Mitigation of Olanzapine induced Cardio Metabolic Syndrome in Rats

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ABSTRACT

Cardiometabolic syndrome was induced by 15 mg/kg Olanzapine (i.p.) weekly suspended in 1% w/v Carboxymethyl cellulose for 28 days in healthy male Sprague Dawley rats. Group I served as normal control. Groups II-VII was given Olanzapine weekly challenge. Group III vehicle control received orally 1% w/v CMC (1ml/kg), Group IV received Metformin (40mg/kg, p.o) and Group V-VII received Ciprofloxacin (CP) (15 mg/kg, 30 mg/kg and 45 mg/kg) for 28 days respectively. After 28 days, following parameters were assessed - Body weight, abdominal circumference and nasal – anus height, Cardiac hypertrophy, mean blood pressure, heart rate and QTc interval, while in serum sample - glucose , oral glucose tolerance test , total cholesterol , triglyceride , low density lipoprotein , very low density lipoprotein , high density lipoprotein and antioxidant: reduced glutathione, superoxide dismutase , catalase, malondialdehyde were estimated. Adiposity index and histological examination of heart was also done. One way analysis of variance followed by post-hoc dunnett's test was performed for statistical analysis with $p<0.05$ set as statistical significance. CP (15 mg/kg, 30 mg/kg and 45 mg/kg) and Metformin (40 mg/kg) treatment precluded change in anthropometric, hemodynamic parameter, biochemical parameter, forbade change in lipid peroxidation and also surged levels of antioxidant as compared to model control. The results were supported by histopathology. Administration of Olanzapine to normal rats for 28 days led to insulin resistance, dyslipidemia, hypertension and oxidative stress. As Ciprofloxacin combated all these abnormalities, it can be used as a novel alternative for current therapies of cardio metabolic syndrome.

Key Words: *Cardiometabolic syndrome, TGR5, Olanzapine, Ciprofloxacin*

INTRODUCTION

Could the increasing prevalence of metabolic syndrome be the "elephant in the room," draining limited healthcare resources? CARDIO METABOLIC SYNDROME, so-called "*deadly quartet*" – a clinical entity of substantial heterogeneity, represented by the co-occurrence of overweight (obesity), high blood pressure, elevated insulin level and lipid metabolism disorder [5].

Epidemiologists in India and International agencies such as the world health organization (WHO) have been sounding an alarm on the rapidly rising burden of cardio metabolic syndrome for the past 10 years. Developed countries like Australia, Europe and America with 48.2 %, 30 – 80 % and 35 % respectively are highly prevalent in hub of cardio metabolic syndrome [1]. But the data doesn't stop at developed countries.

Similar to developed countries, the prevalence is rapidly increasing in developing countries, reflecting the transition from a traditional to a western-like lifestyle : demographic transition (shift to low fertility, low mortality, and higher life expectancy), and epidemiological transition (from widely prevalent infectious diseases to a pattern of a high prevalence of lifestyle related diseases) evolved in developing countries as they become economically more resourcefull leading to significant shifts in dietary and physical activity patterns resulting in cardio metabolic syndrome [3].

In India, Cardio metabolic syndrome is responsible for 2/3rd of the total morbidity burden and about 53% of total deaths (up from 40.4% in 1990 and expected to increase to 59% by 2015) [4]. According to predictions, by 2030 cardio metabolic syndrome will account for almost three quarters of all deaths in India [4].

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Estimates concerning the costs incurred yearly in the developed countries by direct expenses and indirect costs through loss of productivity by polypharmacy therapy account for 40 % of their budget-and this is increasing [2]. Whereas, India is losing more than 6% of its GDP annually due to premature deaths and preventable illnesses, according to a World Bank 2010 report [4]. Oodles of epidemiological studies depict that cardio metabolic syndrome is not only a global burden but also an economic burden.

The pathogenesis of the metabolic syndrome is currently a subject of crucial discussion. The criteria of metabolic syndrome are interrelated, but the path physiology of their relation is not yet fully understood. The long-standing debate about how to define this syndrome led to the appearance of two distinct schools of thought: the insulin resistance-based and the ectopic fat deposition-based hypothesis [5]. As cardio metabolic syndrome is constellation of various metabolic disturbances. Till date, individual pharmacological agents are given for individual metabolic disturbances of cardio metabolic syndrome and thereby increasing public health expenditure, increased drug-drug interaction and low patient compliance. Neither specific agonist nor specific target is discovered for mitigation of cardio metabolic syndrome.

Keeping in mind all the flaws of existing therapy, it becomes the need of the hour to search for specific target and its pharmacological agents that can perhaps treat the root cause of metabolic syndrome.

Literature survey revealed that bile acid (BA) is important regulator of glucose homeostasis, lipid metabolism, and energy expenditure [19, 20].

TGR5 is a recently identified plasma membrane-bound, G protein–coupled receptor for BA [14]. TGR5 is a member of the rhodopsin-like superfamily of G-protein coupled receptors with most important expression levels in gallbladder, ileum and colon [21].

TGR5 activation leads to receptor internalization and liberation of the Gαs subunit, which activates adenylate cyclase subsequently inducing cAMP production and protein kinase A activation (PKA). PKA phosphorylates the cAMP-response element-binding protein (CREB) and induces the transcription of its target genes [22, 23].

In silico screening, docking calculation and in-vitro experiments showed that Ciprofloxacin functions as TGR5 ligand [28]. In light of the above facts, the objective of the present investigation is:

- To evaluate the effect of TGR5 ligand Ciprofloxacin in mitigation of Olanzapine induced cardio metabolic syndrome.

MATERIAL AND METHODS

Material:

Drugs and preparation of solutions:

Olanzapine, Metformin and Ciprofloxacin pure powders were obtained from pharmaceutical suppliers. Olanzapine solution was prepared freshly everyday by suspending the drug in 1% Carboxymethyl Cellulose (CMC) suspension. Whereas Metformin and Ciprofloxacin were prepared freshly everyday by suspending the drug in distilled water

Chemicals and kits:

All the chemicals used in this project were of analytical grade and were obtained from Astron chemicals, Ahmedabad and SD fine chemicals, Mumbai.

All the biochemical tests were performed using the standard kits purchased from Coral chemical systems, Goa.
Phenobarbital ampoules were purchased from krupa medical store, Anand.

Animals:

Healthy male Sprague Dawley rats of 6-8weeks weighing 150 ± 30 were used for the study. The animals were housed in a group of 3 rats per cage under well-controlled conditions of temperature (22 ± 2°C), humidity (55 ± 5%) and 12hrs/12hrs light-dark cycle. Animals had free access to conventional laboratory diet and tap water *ad libitum*.

The protocol of the experiment was approved by Institutional Animal Ethical Committee as per the guidance of the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA), Ministry of Social Justice and Empowerment, Government of India. (Protocol No: APC/2013-IAEC/1320).

Methods:

Experimental procedure:

Dose fixation study:

Three doses were selected for Ciprofloxacin: 15, 30 and 40 mg/kg [29]. No previous studies have been done on metabolic syndrome investigating effect of Ciprofloxacin. Mice doses used for intestinal colitis were converted to rat dose by multiplying it with conversion factor as given in CDER guideline.

Animal Groups:

Animals were randomly allocated based on serum cholesterol levels in 7 groups, with n=6 animals in each group, as follows:
Group I Normal Control were given RO water, Group II Model Control received Olanzapine 1 mg/kg i.p.
Group III Vehicle Control were given 1% CMC solution, Group IV Standard received Metformin 45mg/kg p.o.
Group V- VII received Ciprofloxacin 15 mg/kg i.p., 30 mg/kg i.p. and 60 mg/kg i.p. respectively.

Induction of cardio metabolic syndrome by Olanzapine: [10, 11]

In the present study, 15mg/kg Olanzapine (i.p.) weekly suspended in 1%w/v CMC was given for duration of 28 days to induce metabolic syndrome. Olanzapine mimics the clinical features in animals such as weight gain associated hyperphagia, increased feeding efficiency, adiposity and altered locomotor activity and satiety signaling in 28 days.

The standard drug and investigational drug were administered orally for 28 days.

Parameters:

After 28 days, following parameters were assessed - Body weight, abdominal circumference and nasal – anus height, Cardiac hypertrophy, mean blood pressure [16, 17], heart rate [16, 17] and QTc interval [16, 17].

Collection of Biological sample: Blood:

After completion of 28 days treatment, blood was collected retro-orbitally under anesthetic conditions and animals were sacrificed by Phenobarbital anesthesia. Serum was separated by centrifugation at 3000 rpm for 15 min [12] and was then analyzed for various biochemical parameters : glucose [13], oral glucose tolerance test (OGTT) [13], total cholesterol (TC), triglyceride (TG) [15], low density lipoprotein (LDL), very low density lipoprotein (VLDL) [33], high density lipoprotein (HDL) [14] and antioxidant: reduced glutathione (GSH) [30], superoxide dismutase (SOD) [31], catalase (CAT) [32], malondialdehyde (MDA) [29].

Tissue isolation:

After sacrificing animals, Adiposity index will be assessed & isolated heart was preserved in 10% neutral buffered formalin for histopathology

Statistical Analysis: [18]

Results were presented as mean ± SEM. Statistical analysis of various biochemicals parameters were carried out using the one way analysis of variance (ANOVA) followed by Dunnett's post hoc test. Data were considered statistically significant at $P \leq 0.05$.

RESULTS AND DISCUSSION

Effect on Anthrometeric Parameter:

Olanzapine, H1 antagonism play key role in weight gain since it mediates the orexigenic effects of AMP kinase, an enzyme involved in regulating food intake, while reversing the actions of leptin, an anorexigenic hormone [6].

TGR5 activation induces deiodinase-2 expression in murine brown adipose tissue (BAT) and human skeletal muscle cells by increasing cAMP levels. Deiodinase-2- mediated conversion of inactive thyroxine (T4) to active 3, 5, 3'-tri-iodotyronine (T3) enhances the expression of uncoupling proteins (UCP), mitochondrial oxidative phosphorylation and energy expenditure in BAT and skeletal muscle with a therapeutic implication for obesity [24].

Olanzapine induced animals during the induction period showed gradual incline in the body weight (%), abdominal circumference (mm) & adiposity index compared to the normal control animals. During the treatment, gradual decline in the previously elevated body weight as shown in fig 1 , 2 & 3 respectively.

There was no significant increase in nasal- anus height in model control & treatment animals as compared to normal animals was seen as shown in fig 4.

Effect on Biochemical Parameters:

Oodles of research studies have proved that Olanzapine attenuate insulin signaling pathway, decreased protein levels of IRS2 and of the insulin signaling and glycogen synthesis, diminishing insulin-stimulated AKT and GSK3a/b phosphorylation [7].

Olanzapine in rats showed 191.2% increase in the total glucose levels in the serum of the model control animals compared to the normal control animals.

TGR5 induction of GLP-1 in STC-1 (enteroendocrine) cells is mediated by an increase in cAMP (stimulation of glucose dependant insulin secretion, reduced food intake and reduced lipolysis) [26].

On day 28, glucose levels in model control (241.1±1.13 mg/dl) remained significantly ($P<0.05$) elevated than normal control animals (128.6±1.54 mg/dl).

Treatment with standard metformin (40 mg/kg) and CP (15mg/kg, 30 mg/kg and 45 mg/kg) significantly ($P<0.001$) lessened this elevation in serum glucose levels () (133.5±1.54 mg/dl, 203.9±1.28, 147.5±0.8718 and 141.9±0.663 respectively) as compared to model control as shown in fig 10.*There was deduction in peak level of glucose level after glucose load in all treatment groups as compared to model control animals as shown in fig 11.*

RLP-C is an intermediate metabolite of triglycerides. Under normal conditions; RLP-C is metabolized very rapidly. Lipoprotein lipase activity, hepatic triglylipase activity, and remnant receptor activity are involved in the catabolism of RLP-C. All these enzyme and receptor activities are diminished in the presence of insulin resistance [8].

The percentage boost up in triglyceride, cholesterol, HDL, LDL and VLDL levels in 28 days olanzapine induced rats

were found to be 182.62%, 191.03%, 94.75%, 64.4 % and 138.99% respectively.

TGR5 affects hepatic lipid content. Female TGR5-deficient mice present an increase *in* hepatic fat content especially when fed a high-fat diet. In line, TGR5 activation improves liver function by decreasing steatosis and preventing fibrosis. Additionally, plasma TG and non-esterified fatty acid levels are decreased upon TGR5 activation [25].

CP (15mg/kg, 30mg/kg and 45mg/kg) treatment precluded the rise in triglyceride (80.87, 85.94 and 85.09%), cholesterol (87.25, 90.50 and 92.30%); LDL (58.6%, 61.8 and 64.4%); HDL (43.33, 45.6 and 48.6) VLDL (59.46, 68.42 and 70.21%) which was comparable to metformin (88.68%; 95.31% ; 64.9% ; 30.42056% and 76.14% respectively as shown in fig 6-8 respectively.

Administration of Olanzapine results in increased lipid peroxidation by the induction of free radical production. TGR5 inhibit nuclear factor k light chain enhancer of activated B cells (NF-Kb) activity and the subsequent production of inflammatory cytokines [27].

Malondialdehyde, an end product of lipid peroxidation, is extensively used as a biomarker of lipid peroxidation. Cardio metabolic syndrome model control animals showed higher malondialdehyde (MDA) levels compared to the normal control animals as a result of lipid peroxidation. There was 50% overshoot in MDA levels in the cardio metabolic syndrome model animals compared to the normal control animals. *Metformin (40mg/kg), CP (15 mg/kg), (30 mg/kg) and (45 mg/kg) treatment tend to produce a decline in the MDA levels 10.73%, 17.65%, 21.6% and 29.2%respectively as compared to the model control animal as shown in fig 12.*

Superoxide dismutase (SOD) catalyzes the disputation reaction of the toxic superoxide radicals to molecular oxygen and hydrogen peroxide. Catalase and Glutathione (GSH) promotes the conversion of hydrogen peroxide to water and molecular oxygen. In this study, the activities of CAT, SOD, and GSH were found to be significantly lower in cardio metabolic syndrome, than in normal rats. There was 52% fall in GSH levels in model control animals compared to the normal control animals. *Metformin (40 mg/kg), CP (15 mg/kg), (30 mg/kg), (45 mg/kg) treatment surged the GSH levels 46.28%, 50.1%, 63.9% and 68.1% as compared to the model control animals as shown in fig 13.*

SOD levels showed 30.8% decrease in the model control animals compared to the normal control animals. *Metformin (40 mg/kg), CP (15 mg/kg), (30 mg/kg), (45 mg/kg) treatment inflated the SOD levels 13.3%, 15.2%, 19.4%, 22.1%, 20.16% and 19.1% respectively as compared to the model control animals as shown in fig 14.*

CAT levels in model control animals resulted in 36.5% fall compared to the normal control animals. *Metformin (40 mg/kg), CP (15 mg/kg), (30 mg/kg), (45 mg/kg) treatment also demonstrated increase in the CAT levels 23.4%, 38.8%, 42.7% and 51.3% respectively as compared to the model control animals as shown in fig 15.*

Effect on Cardiovascular Parameter:

It has been reported that increase in heart weight may be due to increased water content, oedematous intramuscular spaces and extensive necrosis of cardiac muscle fibres, followed by the invasion of damaged tissues by inflammatory cells.

Induction of olanzapine caused a 36.21% increase in heart weight in model control animals as compared to normal control animals. 5.893%, 9.107%, 8.036% and 6.25% of reversal in olanzapine induced increase in Heart weight was observed on treatment with Metformin (40 mg/kg), CP (15 mg/kg), (30 mg/kg), (45 mg/kg) when compared to model control animals as shown in fig 16 .

Tachycardia to olanzapine treatment may be mediated via blockade of cardiac muscarinic M cholinergic, can block presynaptic a-adrenoceptors, thus may increase sympathetic activity and indirectly activate the ß-adrenoceptors in the heart to elevate HR. Furthermore, it has been suggested that tachycardia may be induced via the baroreceptor reflex [9].

Finding of the present study were in accordance with the above experimental evidences whereby Induction by olanzapine caused 152.95% a rise in heart rate in model control animals as compared to normal control animals. Whereas treatment with Metformin (40 mg/kg), CP (15 mg/kg), (30 mg/kg), (45 mg/kg) significantly decreased level of heart rate (78.94%, 52.63%, 57.89% and 63.16) as compared to model control animals as shown in fig 17.

The blood pressure rose by 126.32% in 28 days olanzapine induced rats than normal control rats. *Metformin (40 mg/kg), CP (15 mg/kg), (30 mg/kg), (45 mg/kg) normalize blood pressure (56.67%, 26.67%, 40% and 53.33%) thereby preventing olanzapine induced increment in blood pressure as shown in fig 18.*

The QT interval represents the duration of ventricular depolarization and repolarization, and is influenced by Heart rate. Various methods have been applied to determine the rate-corrected QT (QTc) interval, the most widely used being Bazett's formula (QTc=QT/RR, where RR is the time interval between two consecutive R waves in the electrocardiogram)

Sympathetic hyperactivity has been implicated in the risk of QT interval prolongation and cardiac arrhythmias associated with olanzapine.

Induction by olanzapine caused 168.2246% a rise in QT interval in model control animals as compared to normal control animals.92.70, 50.31, 74.5% and 75% of reversal in olanzapine induced rise in QT interval was observed on treatment metformin (40 mg/kg), CP (15 mg/kg), (30 mg/kg), (45 mg/kg) respectively when compared to model control animals as shown in fig 19.

Treatment with *Metformin (40 mg/kg), CP (15 mg/kg), (30 mg/kg), (45 mg/kg) produced significant prevention of marked edema and mild inflammation* as revealed by evidences of histopathological evaluation as compared to model group as shown in fig 20.

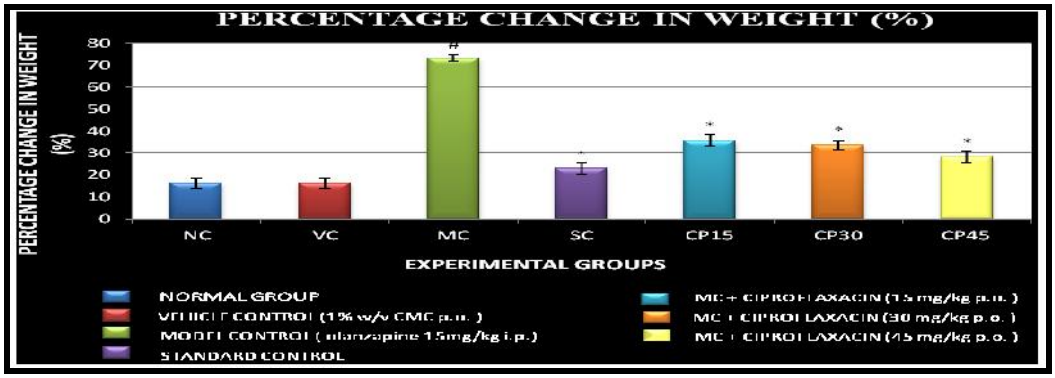


Fig. 1: Effect of Ciprofloxacin on body weight in Olanzapine induced Cardio metabolic syndrome in rats.

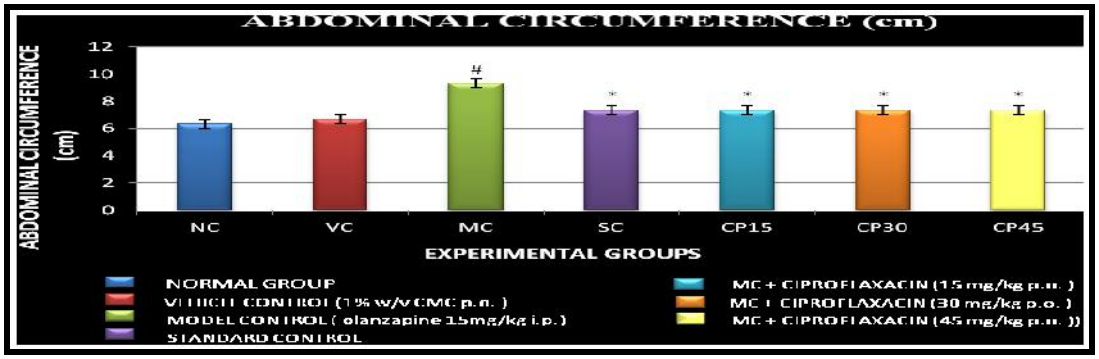


Fig. 2: Effect of Ciprofloxacin on abdominal circumference in Olanzapine induced Cardiometabolic syndrome in rats.

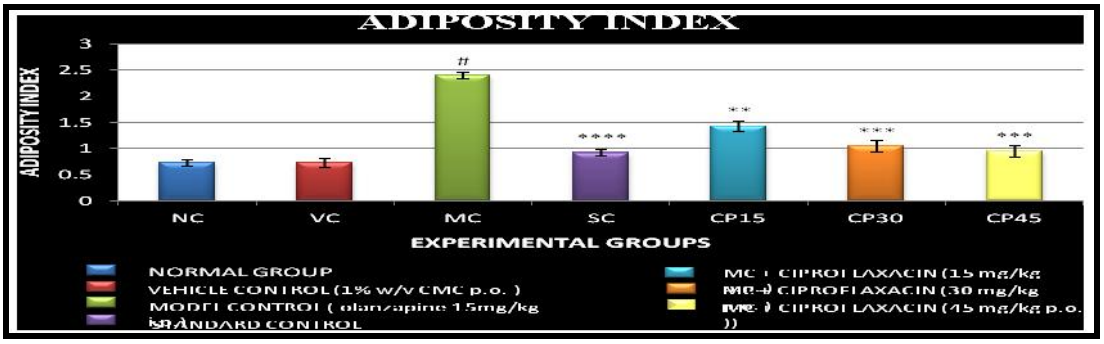


Fig. 3: Effect of Ciprofloxacin on adiposity index in Olanzapine induced Cardio metabolic syndrome in rats.

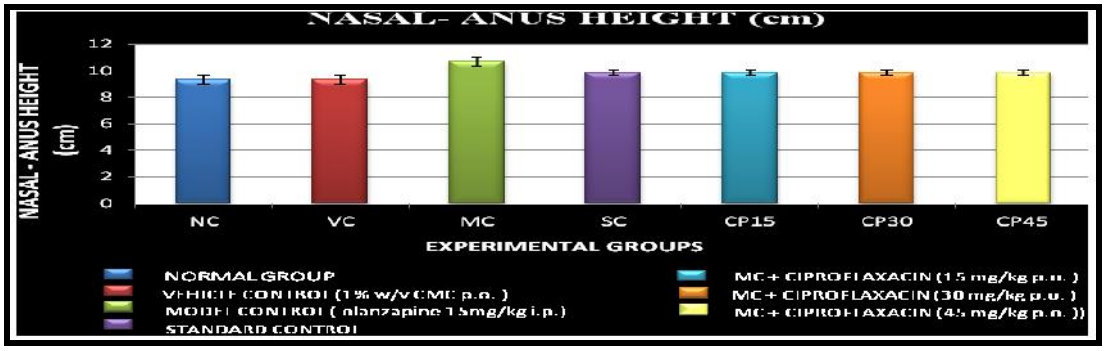


Fig. 4: Effect of Ciprofloxacin on nasal - anus height in Olanzapine induced Cardio metabolic syndrome in rats.

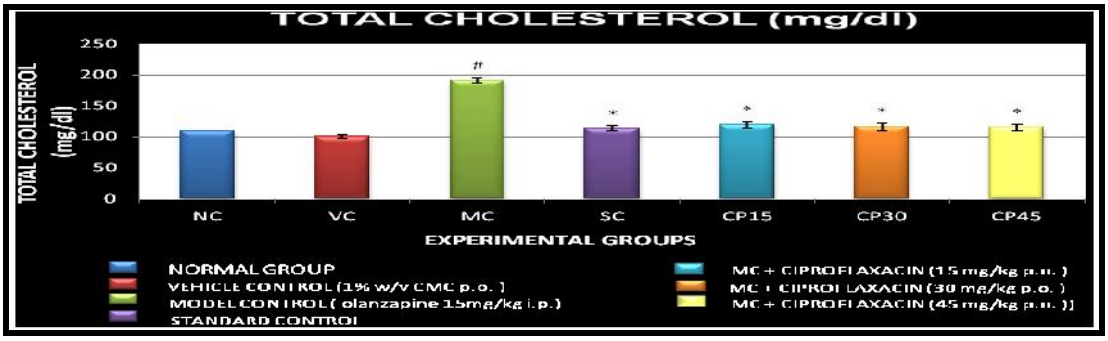


Fig. 5: Effect of Ciprofloxacin on serum total cholesterol levels in Olanzapine induced Cardio metabolic syndrome in rats.

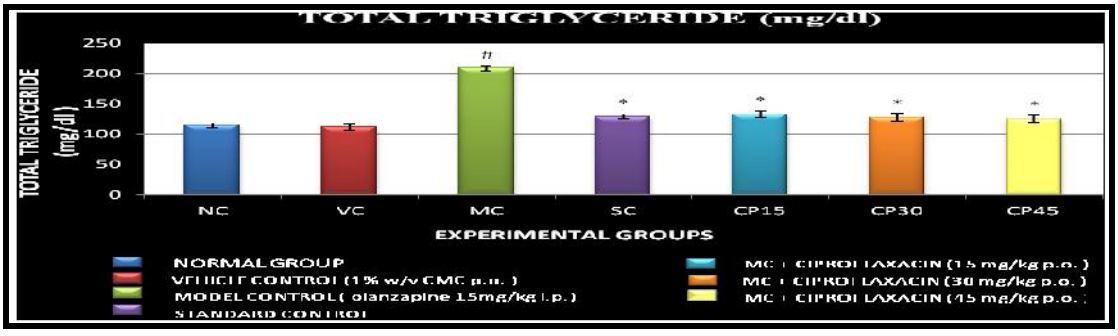


Fig. 6: Effect of Ciprofloxacin on serum total triglyceride levels in Olanzapine induced Cardio metabolic syndrome in rats.

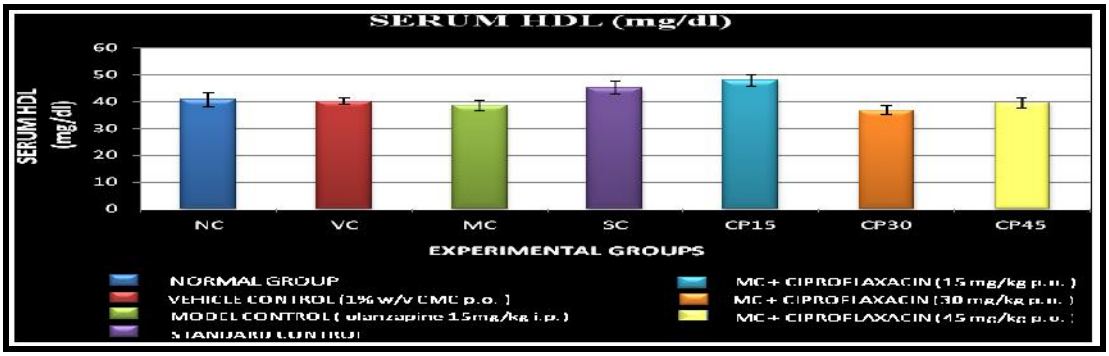


Fig. 7: Effect of Ciprofloxacin on serum HDL levels in Olanzapine induced Cardio metabolic syndrome in rats.

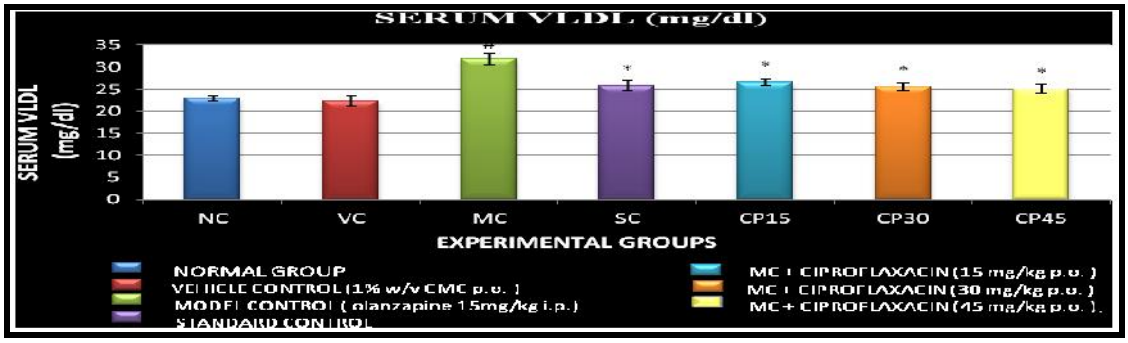


Fig. 8: Effect of Ciprofloxacin on serum VLDL levels in Olanzapine induced Cardio metabolic syndrome in rats.

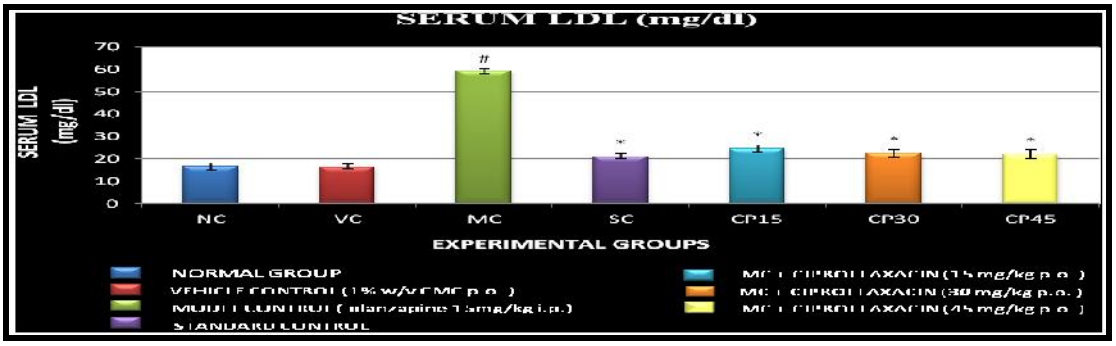


Fig. 9: Effect of Ciprofloxacin on serum LDL levels in Olanzapine induced Cardio metabolic syndrome in rats.

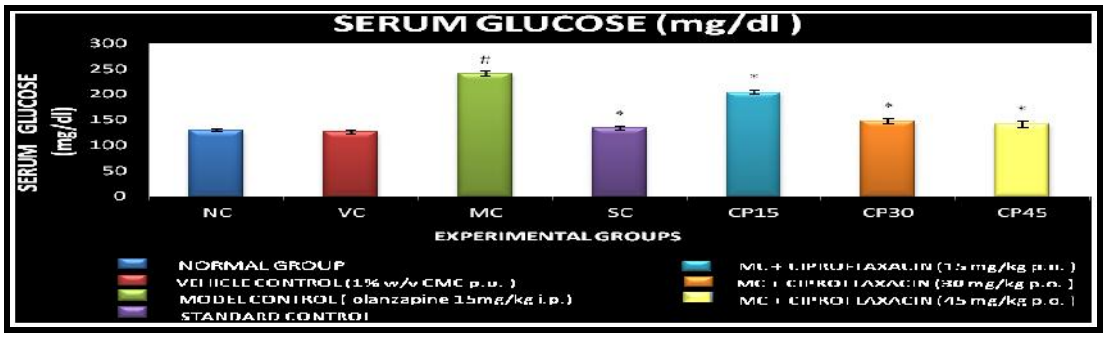


Fig. 10: Effect of Ciprofloxacin on serum GLUCOSE levels in Olanzapine induced Cardio metabolic syndrome in rats.

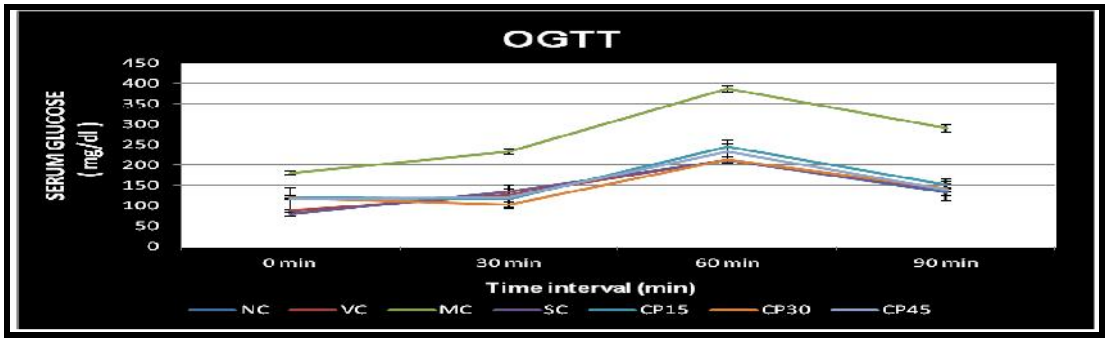


Fig. 11: Effect of Ciprofloxacin on serum GLUCOSE levels in Olanzapine induced Cardio metabolic syndrome in rats.

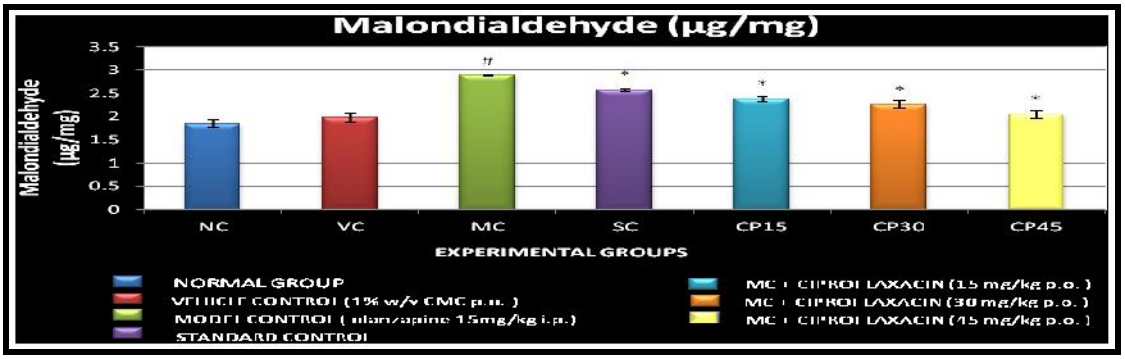


Fig. 12: Effect of Ciprofloxacin on malondialdehyde (MDA) levels in Olanzapine induced Cardio metabolic syndrome in rats.

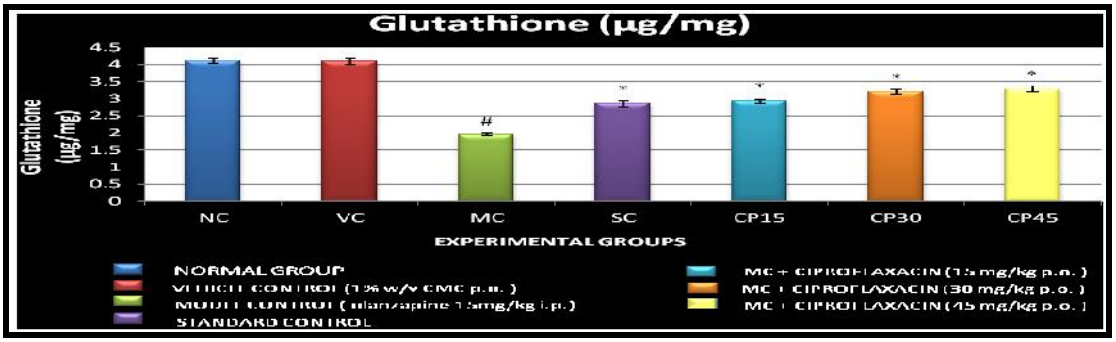


Fig. 13: Effect of Ciprofloxacin on glutathione (GSH) levels in Olanzapine induced Cardio metabolic syndrome in rats.

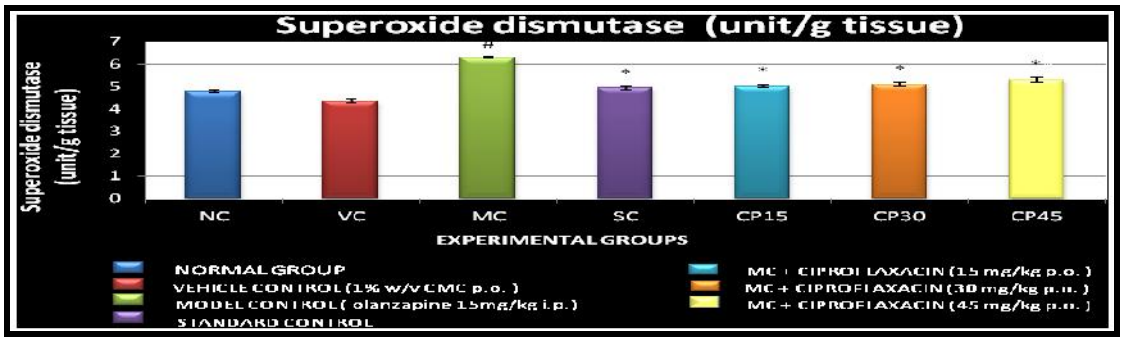


Fig. 14: Effect of Ciprofloxacin on superoxide dismutase (SOD) levels in Olanzapine induced Cardio metabolic syndrome in rats.

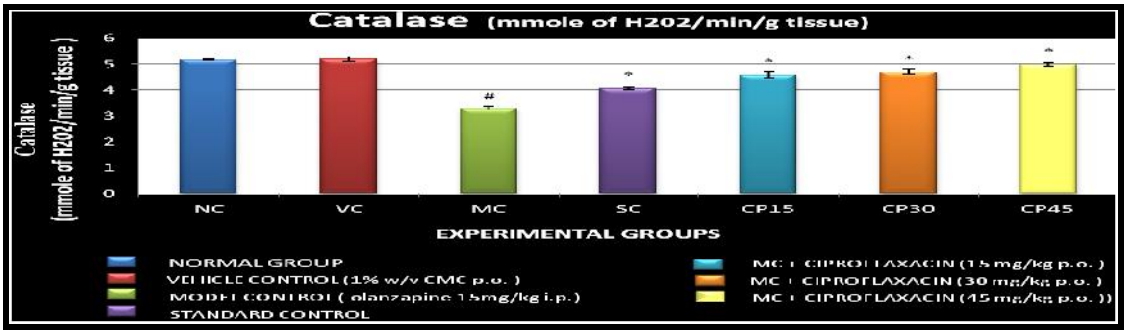


Fig. 15: Effect of Ciprofloxacin on catalase (CAT) levels in Olanzapine induced Cardio metabolic syndrome in rats.

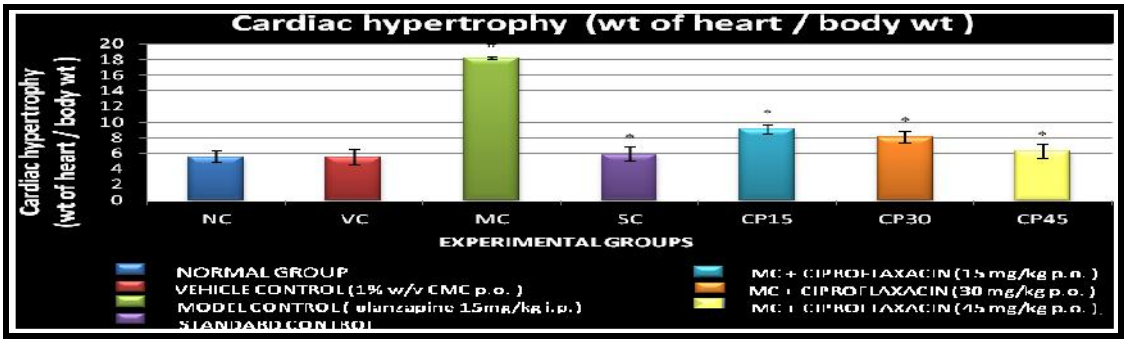
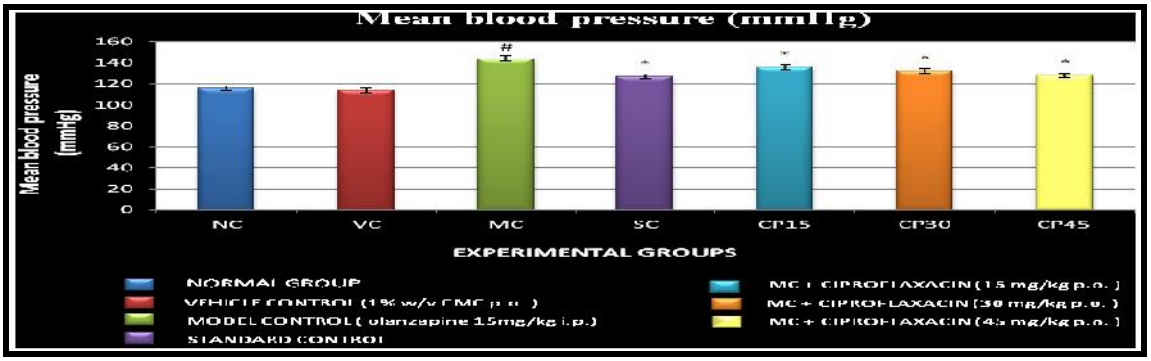
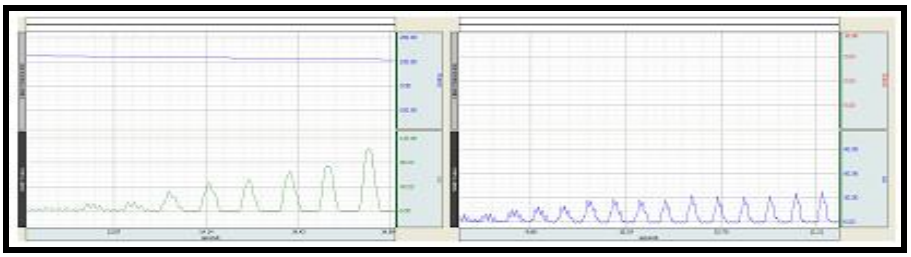
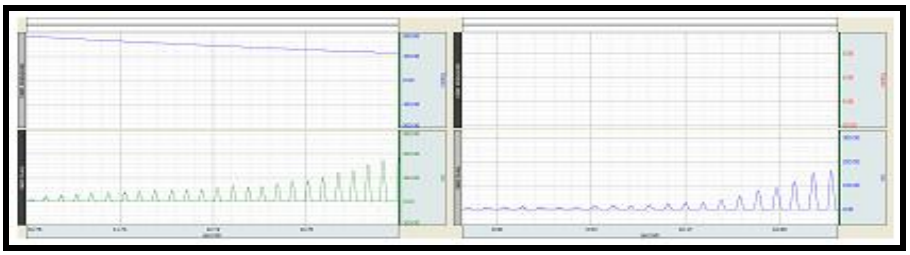


Fig 16: Effect of Ciprofloxacin on cardiac hypertrophy in Olanzapine induced Cardio metabolic syndrome in rats.

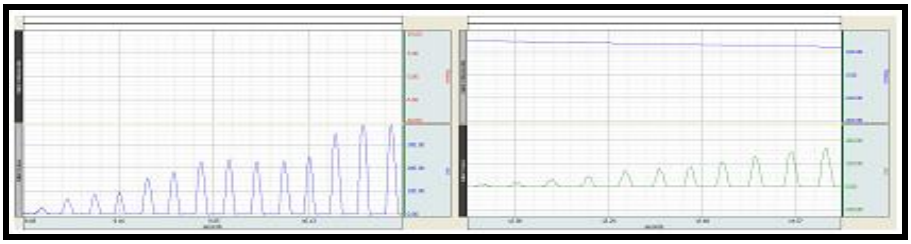




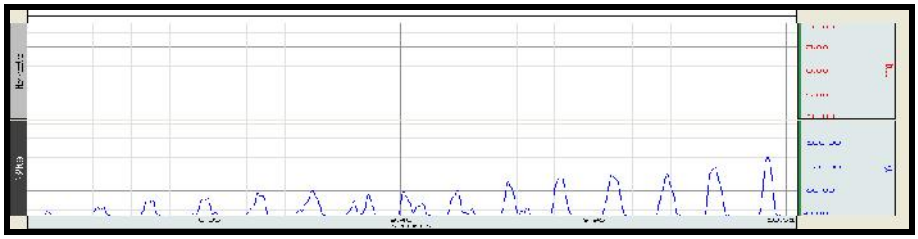
NORMAL GROUP VEHICLE CONTROL



MODEL CONTROL STANDARD CONTROL (40mg/kg)



CP15 (15 mg/kg) CP30 (30mg/kg)



CP 45(45 mg/kg)

Fig. 17: Effect of Ciprofloxacin on mean blood pressure (mmHg) in Olanzapine induced Cardio metabolic syndrome in rats.

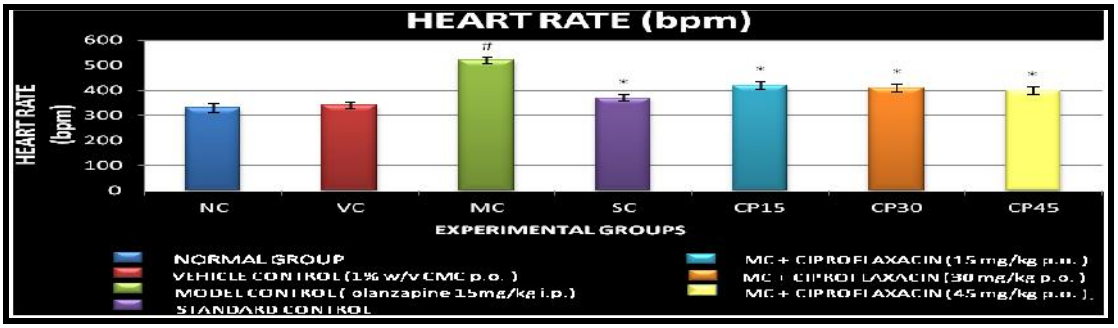
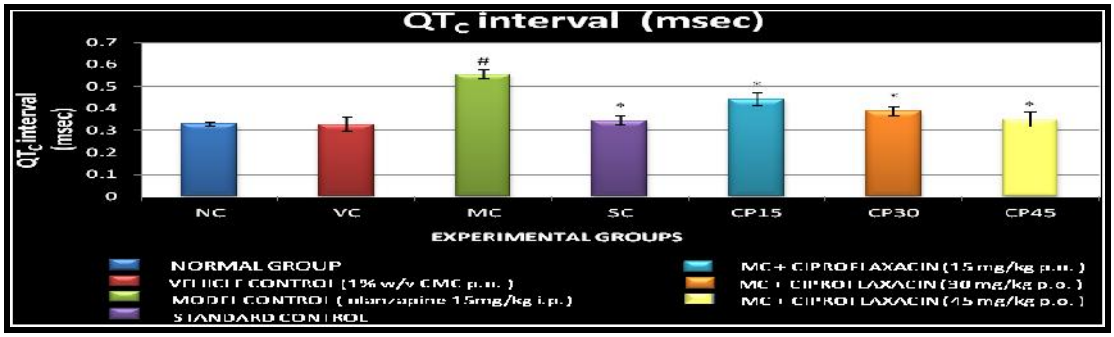
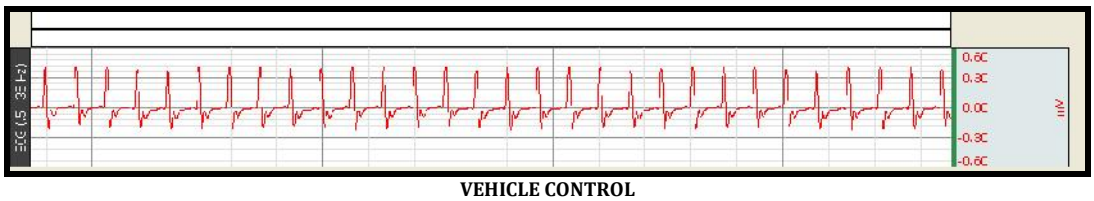


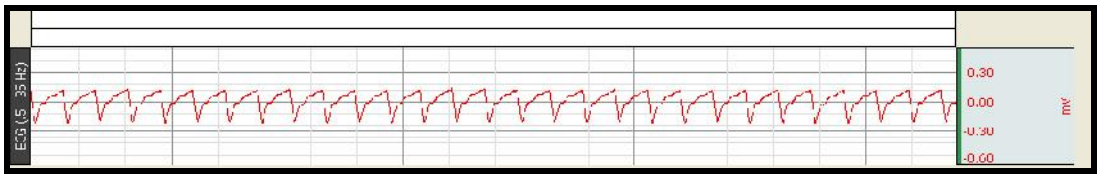
Fig. 18: Effect of Ciprofloxacin on heart rate (bpm) in Olanzapine induced Cardio metabolic syndrome in rats.



NORMAL GROUP

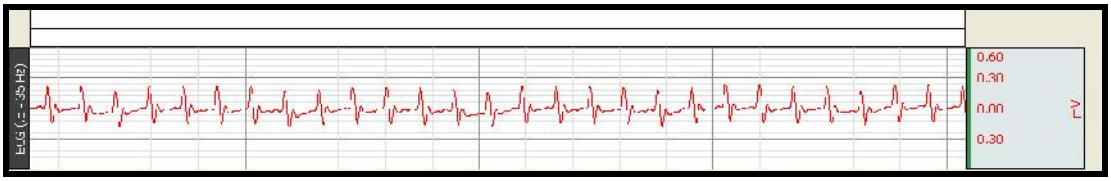


VEHICLE CONTROL



MODEL CONTROL

STANDARD CONTROL



CP 15 (15mg/kg)

CP 30 (30mg/kg)

CP 45 (45 mg/kg)

Fig. 19: Effect of Ciprofloxacin on QT_C interval in Olanzapine induced Cardio metabolic syndrome in rats

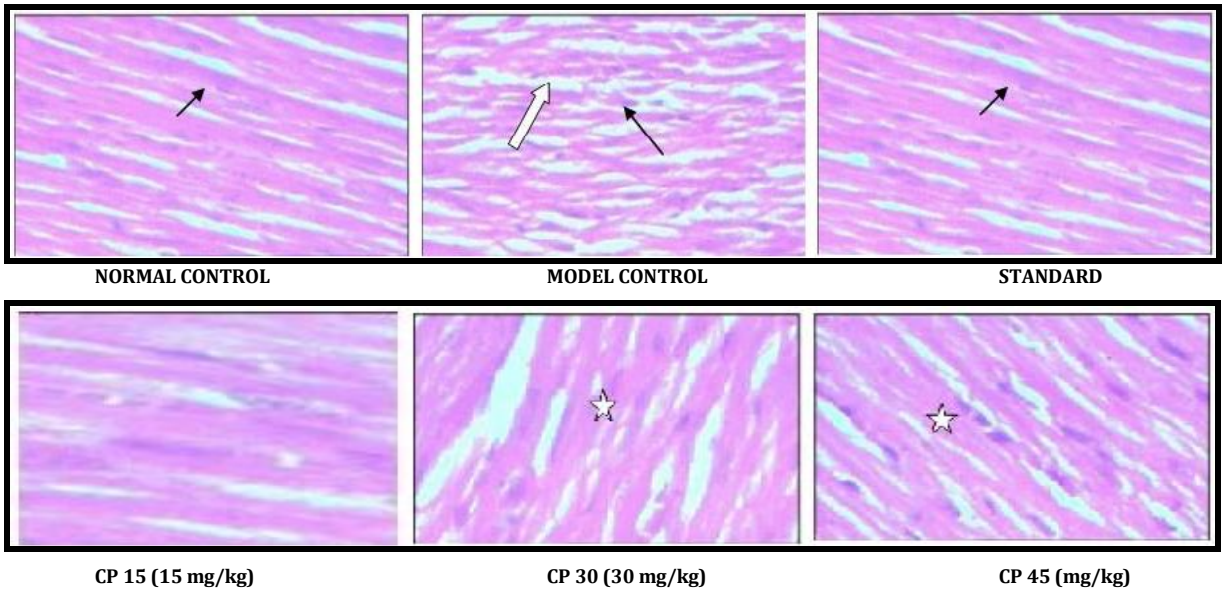


Fig. 20: Photographs of hematoxyline & eosin stained paraffin sections of rat hearts.

SUMMARY AND CONCLUSION

Insulin resistance, hypertension, dyslipidemia and disruption of normal balance between oxidative and anti-oxidative process were observed in olanzapine induced rats as compared to normal control animals.

Metformin (40mg/kg), CP (15 mg/kg), (30 mg/kg) and (45 mg/kg) treatment debased percentage change in weight, abdominal circumference, nasal-anus height and adiposity index compared to the model control animals.

Glucose level for Metformin (40mg/kg), CP (15 mg/kg), (30 mg/kg) and (45 mg/kg) treatment were found to be lessened compared to the model control animals.

There was also deduction in peak level of glucose level after glucose load in all treatment groups as compared to model control animals.

Metformin (40mg/kg), CP (15mg/kg, 30mg/kg and 45mg/kg) treatment precluded the rise in triglyceride, cholesterol, LDL and VLDL which was comparable to model control animals.

All treatment group forbade change in lipid peroxidation; surged levels of GSH, SOD and CAT inhibiting detrimental effect of free radical on lipid peroxidation and enzymes antioxidants as compared to model control animals

Induction by olanzapine caused a rise in cardiac hypertrophy, mean blood pressure, heart rate and QTc interval in model control animals as compared to normal control animals. Reported result demonstrated a reversal in olanzapine induced cardiac hypertrophy, mean blood pressure, heart rate and QTc interval rise in treatment group of metformin (40 mg/kg) and CP (15 mg/kg), (30 mg/kg), (45 mg/kg).

Treatment with Metformin (40 mg/kg), CP (15 mg/kg), (30 mg/kg), (45 mg/kg) produced significant prevention of marked edema and mild inflammation as revealed by evidences of histopathological evaluation as compared to model group.

In conclusion, induction by olanzapine to normal rats for 28 days led to insulin resistance, dyslipidemia, hypertension and oxidative stress. Ciprofloxacin combat all these abnormalities and can be used as an alternative for current therapies of cardio metabolic syndrome.

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