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PROTECTIVE EFFECT OF IVERMECTIN IN HIGH FAT HIGH CARBOHYDRATE DIET AND OLANZAPINE INDUCED METABOLIC SYNDROME IN RATS

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ABSTRACT

Background: Metabolic syndrome is a cluster of cardiovascular risk factors, including abdominal obesity, hyperglycemia, elevated blood pressure and dyslipidemia. Bile acid regulating receptor farnesoid X receptor plays significant role in treating disorder of glucose and lipid homeostasis. In silico screening, docking and in-vitro experiments have shown that ivermectin functions as FXR ligand. Objective: This study aimed to investigate the effect of ivermectin in high fat high carbohydrate diet (HFHC) induced metabolic syndrome in experimental rats. Experimental work: Metabolic syndrome was induced by administration of olanzapine (15 mg/kg i.p.) once in a week and HFHC for four weeks followed by HFHC alone for next eight weeks. The rats were divided into three groups: (I) Control group (II) Model control (olanzapine (15 mg/kg, i.p.) and HFHC diet) (III) Treatment group was administered Olanzapine (15 mg/kg, i.p.) and HFHC diet + Ivermectin (0.6 mg/kg, p.o.). Result: HFHC control animals developed the signs of metabolic syndrome including elevated abdominal fat deposition, impaired glucose tolerance,

hypertension, altered lipid profile (TG, TCHL, LDL, HDL, and VLDL), Liver profile (ALT, AST and ALP) and increased oxidative stress markers. The analysis of left ventricular function (LVEDP, dp/dt_{max}., dp/dt_{min}) presented promising results. Ivermectin treatment prevented elevation in blood glucose, blood pressure, oxidative stress and ameliorated lipid profile, liver profile and glucose tolerance indicating the protective effect of ivermectin in improving of lipid, liver enzyme and glucose levels. Furthermore, histopathological studies also indicates that ivermectin ameliorates MS. Conclusion: Ivermectin could be a promising candidate for combatting metabolic syndrome.

Keywords: Metabolic syndrome, FXR, Olanzapine, High fat high carbohydrate (HFHC) diet, Ivermectin

1.0 INTRODUCTION:

Metabolic syndrome (MS) is group of metabolic disorders like glucose intolerance which consist of hyperinsulinemia/insulin resistance, hypertension, central obesity, and dyslipidemia. MS is an escalating global problem, with an increasing prevalence in urban populations of some developing as well as developed countries **[1]**. An approach which can target these complications should be selected. It is important to establish single therapy concept that decrease the incidence of metabolic syndrome. The bile acid receptor Farnesoid X receptor (FXR) regulate lipid, glucose, and energy metabolism, regulate lipid, glucose, and energy metabolism, proving to be a potential pharmacological target for MS therapy **[2]**. FXR is one of the most important member of the nuclear receptor superfamily and is expressed in liver, intestine, adipose tissue and the vascular wall and is emerged as an important player in the control of various metabolic pathways.[3] FXR is activated by bile acids. On its activation by bile acids, FXR regulates bile acid synthesis, conjugation, and transport, as well as various aspects of lipid and glucose metabolism. FXR decreases triglyceride levels, LDL levels and cholesterol**.** FXR activation may improves peripheral insulin sensitivity and promotes glycogen synthesis. FXR has been explored in cholestasis, diabetes mellitus type II and metabolic syndrome, nonalcoholic steatohepatitis (NASH) or nonalcoholic fatty liver disease (NAFLD), inflammatory bowel disease and colorectal cancer **[4]**. Thus upon modulation, FXR can be attractive target for metabolic syndrome. In silico screening, docking calculation and in-vitro experiments have shown that Ivermectin (IVM) functions as FXR ligand **[5]**. IVM is most commonly used antiparasitic drug. Drug repurposing of IVM

can prove to be efficient single drug treatment option for various risk factors in MS. IVM has been shown to regulate glucose and improves insulin sensitivity and cholesterol levels in diabetic mice **[6]**. Repurposing of IVM for malaria **[7]**, dengue **[8]** and recently, clinical trials have showed promising results of IVM in terms of symptomatology as well as viral load reduction in COVID 19 **[9]**. Thus aim of present study was to determine the protective effect of IVM as a bile acid activating receptor FXR agonist in experimental animals.

2.0. MATERIALS AND METHODS

2.1.Drugs and preparation of solutions:

Olanzapine and IVM pure powder were obtained from Intracin Pharmaceuticals private limited Nadiad, Gujarat, India. Olanzapine and IVM solutions were prepared freshly every day by making suspension of the drug in 0.5 % Carboxy Methyl Cellulose (CMC).

Dose: IVM dose (0.6 mg/kg) was fixed from the preliminary study done at our laboratory using therapeutic doses 0.2 mg/kg, 0.6 mg/kg and 1.8 mg/kg in diabetic dyslipidemia amongst which 0.6 mg/kg had shown promising results

Chemicals and kits:

All the Chemicals used in this project were of analytical grade and were procured from Astron chemicals, Ahmedabad and SD fine chemicals, Mumbai. All the biochemical tests were performed using the standard kits purchased from Span Diagnostics Pvt. Ltd., India.

2.2.Experimental Animals and protocol approval:

Healthy male Sprague-dawley rats of 6-8weeks weighing 150 ± 10 were used for the study. All experimental animals were housed under controlled environment of temperature (22 ± 2°C), Humidity (55 ± 5%), 12-h-light/-dark cycle. The animals had free access to water *ad libitum* and standard laboratory diet for normal control (purchased from Pranav Argo Pvt. Ltd). The experimental protocol was approved by IAEC (Institutional Animal Ethical Committee) as per the guidance of the CPCSEA (Committee for the Purpose of Control and Supervision of Experiments on Animals) Ministry of Social Justice and Empowerment, Government of India. (Protocol no: APC/2016-IAEC/1623).

2.3.Induction of metabolic syndrome:

For induction of metabolic syndrome, Olanzapine (15mg/kg, i.p.) was given weekly for duration of 28 days (4 weeks) **[10]** along with high fat high carbohydrate diet (HFHC)

for the duration of 90 days (12 weeks). The composition of the HFHC diet was referred from Panchal *et al*. **[11]**

2.4.Experimental Design:

Healthy Sprague dawley rats (n= 30) were randomized based on the body weight into three following groups: Normal Control (n=10): received vehicle (0.5% CMC) orally and standard rat diet for the duration of 90 days; Model Control (n=10): received Olanzapine 15 mg/kg i.p (weekly for 28 days) and HFHC diet for duration of 90 days; Treatment Control (n=10): received IVM 0.6 mg/kg p.o, Olanzapine 15 mg/kg i.p. (weekly for 28 days) and HFHC diet for the duration of 90 days.

2.5.Physiological measurements

Body weight of each animal was measured weekly. Food and water intakes were recorded daily for all rats per cage and the average was calculated. Abdominal circumference was measured on 90th day by standard measuring tape.

2.6.Blood Pressure

Blood pressure was measured using NIBP 200A small animal tail noninvasive blood pressure system (BIOPAC System, Inc.). The tracing were analyzed using Acknowledge 4.2.software.

2.7.Oral Glucose Tolerance test (OGTT)

The rats were deprived of food for overnight fasting (12 hour). The rats were given glucose load of 2 g/kg body weight as 40% glucose solution through oral gavage and blood glucose concentrations were measured by tail vein blood sample at 0, 30, 60, 90, and 120 minutes after oral glucose administration using Arkray glucometer.

2.8.Biochemical parameters in serum

The rats were anesthetized and blood samples were collected on 90th day from the eye through retro-orbital plexus muscle using ketamine (50mg/kg) and xylazine (10mg/kg) i.p. as an anesthetic agent. The estimation of glucose, triglyceride (TG), total cholesterol (TCHL), low density lipoprotein (LDL), high density lipoprotein (HDL), very low density lipoprotein (VLDL), aspartate aminotransferase (AST), alanine aminotransferase (ALT), Alkaline phosphatase (ALP) and total bilirubin (TB) were performed in serum samples using commercially available standard enzymatic kits (Span Diagnostics Pvt. Ltd., India).

2.9.Langendorff Isolated Perfused Heart Preparation

Perfusion of isolated hearts was performed according to the Langendorff technique. The hearts were excised after thoracotomy and tied to the aortic cannula. Hearts were

perfused with modified Krebs-Henseleit buffer (composition: CaCl2 (1.5 mM), KCl (4.7 mM), KH2PO4 (1.18 mM), MgSO4 (1.66 mM), NaCl (118 mM), NaHCO3 (24.88 mM), glucose (5.55 mM), Na-pyruvate (2 mM), and bovine albumin (0.1%w/v)). The buffer was filtered by 0.45 μm membrane filter before use. The cannulated heart was rapidly connected with the Langendorff perfusion apparatus (flow rate of buffer: 9.7 ± 0.5 ml/min; carbogen (95% O2 and 5% CO2), and temperature: 37˚C). A latex balloon filled with 50% methanol was tied to the end of a polyethylene tube connected to the pressure transducer and was inserted into a left ventricle of the isolated heart. The diastolic pressure of 5 to 6 mmHg was adjusted and after 30 minutes, various parameters were measured. Parameters measured included dP/dtmax (rate of maximum LV pressure rise); dP/dtmin (rate of minimum LV pressure fall) and Left ventricular end-diastolic pressure (LVEDP) as measurements of relaxation. The data was recorded by physiological recording system and Biopac recording device (MP-36 Biopac Systems, Inc., USA). **[12]**

2.10. Oxidative stress marker parameters (Liver Tissue)

Liver tissue was excised immediately and rinsed in ice-chilled normal saline and the whole liver was weighed. A known weight of liver tissue was taken and homogenized (EIE Instruments Pvt Ltd, 0603121) in 5.0 mL 0.1 M Tris- HCl buffer (pH 7.4). The homogenate was centrifuged at 10,000 rpm for 15 min using the Remi C-24 (high-speed cooling) centrifuge and the supernatant was used for estimation of indicator of lipid peroxidation (MDA assay), Superoxide dismutase (SOD), Catalase and glutathione (GSH).

2.11. Histopathology

Liver and heart were fixed in 10 % neutral buffered formalin and were embedded in paraffin wax. These tissues were sliced in thin sections (5 μm) and stained with haematoxylin and eosin (H & E) for the determination of morphological change.

2.12. Statistical Analysis

All the data are presented as mean ± SEM. Statistical analysis of biochemical parameters, LV functions parameters and oxidative stress marker parameters were carried out using one-way analysis of variance (ANOVA) followed by Dunnett's post hoc test. (Prism, GraphPad version 6.01,

GraphPad Software, Inc.). Data were considered statistically significant at P≤0.05.

3.0. RESULTS

3.1. Effect of IVM on physiological parameter in olanzapine and HFHC diet induced MS in rats.

Significant increase in body weight of model control rats was observed compared to that with normal control rats till 11th week followed by decline in the body weight. Treatment control depicted significant reduction in the weight gain as compared to the model control group rats. **(Figure 1)**.

Table 1 presented the effect on physiological parameters. Food intake and water intake was decreased significantly (P≤0.0001) in the model control group compared to the normal control group. Animals treated with IVM showed significantly higher food (P≤0.01) and water intake (P≤ 0.05) when compared to the model control group. Abdominal circumference was higher in model control animals. Treatment control had shown significant decrease in both the parameters as compared to the model control group.

3.2. Effect of IVM on Haemodynamic parameters on olanzapine and HFHC diet induced MS in rats.

Animals given olanzapine and HFHC diet showed significant rise in blood pressure compared to the normal control group (149.5±1.37 and 100.0±1.15 respectively). Treatment group showed significant decrease in blood pressure in each interval (110.7±2.72) **(Figure 2)**.

Model control showed significant increase in left ventricular end-diastolic pressure (LVEDP) compared to normal group (50.82± 0.71 and 7.145± 0.18 mm Hg respectively), indicating LV haemodynamic overload. On the contrary, treatment with IVM improved both the heart functions Coronary flow rate, dp/ dt max and dp/dt min compared with the model control **(Table 2)**.

3.3. Effect of IVM on serum glucose profile, lipid profile, liver profile in olanzapine and HFHC diet induced MS in rats.

Animals showed significant rise on 90th day in blood glucose, triglyceride, cholesterol, LDL, VLDL, AST, ALT, ALP and total bilirubin in model group when compared to normal control. Significant decline in the levels of HDL in model control group was observed. Ivermectin treated animals showed significant decrease in the levels of glucose, triglyceride, total cholesterol, LDL, VLDL, AST, ALT, ALP and total bilirubin 90th day **(Table 3)**.

3.4. Effect of IVM on OGTT levels in Olanzapine and HFHC diet induced MS in rats.

In OGTT, glucose level at 0 min, 30 min, 60 min, 90 min and 120 min in model control remained significantly ($P<0.05$) elevated than normal control animals. Treatment group Ivermectin (0.6 mg/kg) significantly decreased this elevation in glucose levels at 0 min, 30 min, 60 min, 90 min and 120 min as compared to model control as shown in the **Figure 3**.

3.5. Effect of IVM on Malondialdehyde, Glutathione, Superoxide dismutase and catalase on olanzapine and HFHC diet induced MS in rats.

Lipid peroxidation of model control animals significantly increased the malondialdehyde (MDA) levels compared to normal control animals. Antioxidant enzymes GSH, SOD and CAT levels were significantly decreased (4.29±0.08, 0.007±0.001, 0.07±0.01, respectively). Animals treated with Ivermectin (0.6 mg/kg) presented significant decrease lipid peroxidation levels (0.13±0.21) and significant increase in GSH, SOD and CAT levels (6.38±0.08, 0.017±0.000 and 0.32±0.06) **(Table 4)**.

3.6. Effect of IVM on histopathology of heart and liver on olanzapine and HFHC diet induced MS in rats.

Microscopic histology revealed that the normal group heart and liver was characterized by an organized pattern and shows normal architecture of the myocardium and hepatocytes respectively. Olanzapine and HFHC induced metabolic heart demonstrated marked edema and mild inflammation as compared to normal group heart. model control group, showed fatty changes and enlarged vacuoles in liver as compared to normal control group, all these changes were reversed by ivermectin **(Figure 4)**.

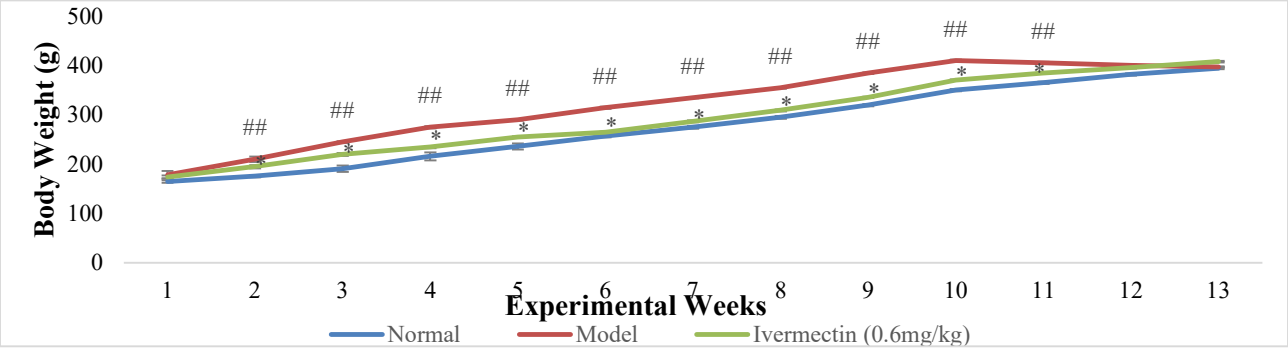


Figure 1: Effect of IVM on change in weight (g) in Olanzapine and HFHC diet induced MS in rats.
Data are expressed are as mean ± SEM (n=10). ## indicates significant difference from normal control P≤0.01; * indicates significant difference from model control P≤0.05.

Table 1: Effect of IVM on physiological parameters in olanzapine and HFHC diet induced MS in rats

Physiological Variable	Normal Control	Model Control	Ivermectin (0.6mg/kg)

Food Intake (g/day)	**29.70±0.51**	**21.70±0.65 (####)**	**24.90±0.75 (**)**
Water Intake (ml/day)	**38.70±1.73**	**22.70±1.16 (####)**	**28.10±1.88 (*)**
Abdominal circumference (cm)	**16.39±0.15**	**17.83±0.10**	**16.90±0.18**

Data are expressed are as mean ± SEM (n=10). #### indicates significant difference from normal control P≤0.0001; * indicates significant difference from model control P≤0.05; ** indicates significant difference from model control P≤0.01.

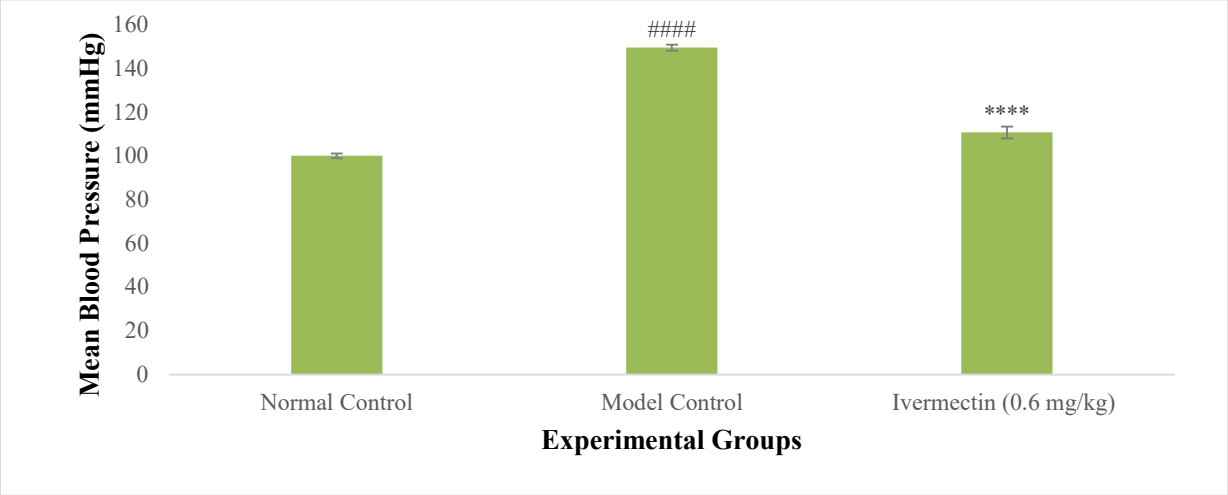


Figure 2: Effect of IVM on mean blood pressure (mmHg) in Olanzapine and HFHC diet induced MS in rats.
Data are expressed are as mean ± SEM (n=10). #### indicates significant difference from normal control P≤0.0001; ** indicates significant difference from model control P≤0.0001**

Table 2: Effect of IVM on coronary flow rate, LVEDP, dp/dt_{max}, dp/dt_{min} in olanzapine and HFHC diet induced MS in rats.

Groups	LVEDP (mmHg)	Coronary flow rate	dp/dt max (mmHg/s)	dp/dt min (mmHg/s)
Normal control	**7.145± 0.18**	**18.2± 0.37**	**3095± 57.69**	**2343± 101.8**
Model control	**50.82± 0.71 (####)**	**12.0± 0.23 (####)**	**1586± 33.45 (####)**	**1092± 37.17 (####)**
Ivermectin (0.6mg/kg)	**10.87±0.43 (****)**	**15.89± 0.26 (****)**	**2162± 33.13 (****)**	**1785±18.32 (****)**

Data are expressed are as mean ± SEM (n=10). #### indicates significant difference from normal control P≤0.0001; ** indicates significant difference from model control P≤0.0001**

Table 3: Effect of IVM on blood glucose profile, lipid profile, liver profile on olanzapine and HFHC induced MS in rats

Parameter	Normal control	Model control	Ivermectin (0.6mg/kg)
Serum Glucose (mg/dl)	**133.4±1.87**	**394.9±12.69 (####)**	**205.8±1.79 (****)**
Triglyceride (mg/dl)	**68.25±1.13**	**252.6±12.20 (####)**	**123.3±4.83 (****)**
Cholesterol (mg/dl)	**79.65±1.45**	**167.30±7.06 (####)**	**118.7±1.88 (****)**
LDL (mg/dl)	**90.33±1.45**	**117.80±7.06 (####)**	**106.64±1.88 (***)**
HDL (mg/dl)	**24.33±1.79**	**1.02±1.19 (####)**	**12.60±0.36 (****)**
VLDL (mg/dl)	**13.65±1.13**	**50.52±12.2 (####)**	**24.66±4.83 (****)**
AST (U/L)	**32.90±1.19**	**124±1.56 (####)**	**92.50±0.69 (****)**
ALT (U/L)	**52.80±0.11**	**145.40±4.76 (####)**	**95.04±2.59 (****)**

ALP (U/L)	**67.15±0.19**	**173.30±0.48 (####)**	**137.70±1.09 (****)**
Total Bilirubin (mg/dl)	**0.36±0.14**	**3.88± 1.21 (####)**	**0.70±1.04 (****)**

Data are expressed are as mean ± SEM (n=10). #### indicates significant difference from normal control P≤0.0001; * indicates significant difference from model control P≤0.001; **** indicates significant difference from model control P≤0.0001**

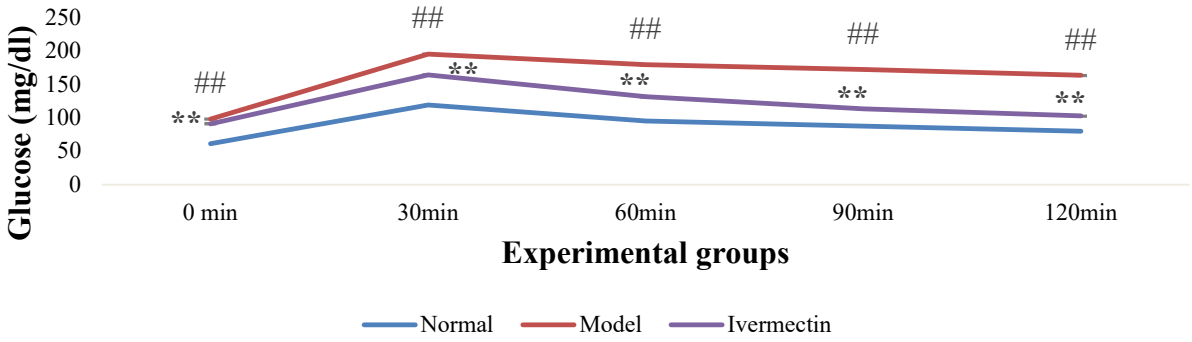
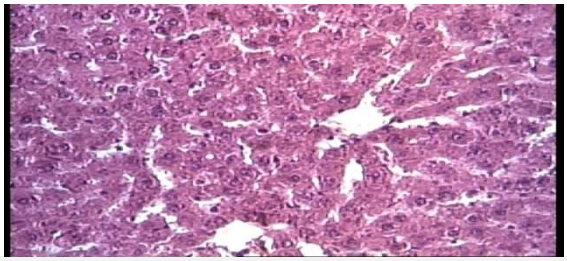


Figure 3: Effect of IVM on OGTT in Olanzapine and HFHC diet induced MS in rats.
The values expressed are as mean ± SEM (n=10). ##indicates significant difference from normal control P≤0.01;indicates significant difference from model control P≤0.01**

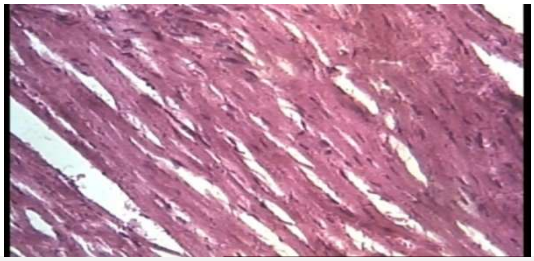
Table 4: Effect of IVM on anti- oxidant parameters in olanzapine and high fat high carbohydrate induced MS in rats.

Parameters	Normal Control	Model Control	Ivermectin (0.6mg/kg)
Malondialdehyde (MDA)	**0.07±0.30**	**0.37±0.24 (####)**	**0.13±0.21 (****)**
Glutathione (GSH)	**8.44±0.24**	**4.29±0.08 (####)**	**6.38±0.08 (****)**
Superoxide dismutase (SOD)	**0.03±0.002**	**0.007±0.001 (####)**	**0.017±0.000 (****)**
Catalase (CAT)	**0.56±0.10**	**0.07±0.01 (####)**	**0.32±0.06 (****)**

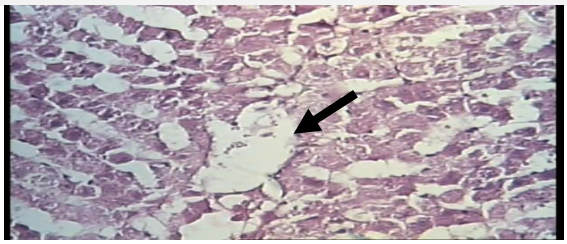
The values expressed are as mean ± SEM (n=10). #### indicates significant difference from normal control P≤0.0001; ** indicates significant difference from model control P≤0.0001**



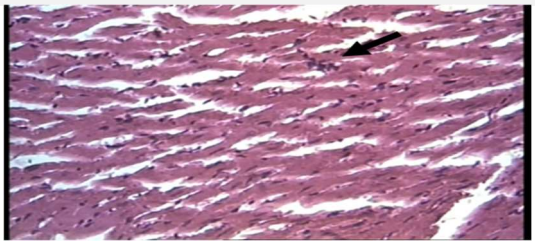
Control group liver



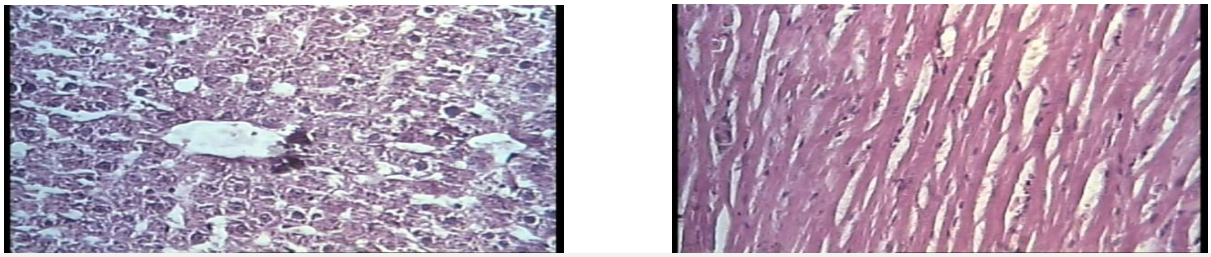
Control group heart



Model control liver



Model control heart



Ivermectin (0.6mg/kg) treated liver Ivermectin (0.6mg/kg) treated heart

Figure 4: Effect of IVM on Histopathological changes in heart and liver tissue in Olanzapine and HFHC diet induced MS in rats. Hematoxylin and eosin staining of heart and liver sections are shown at (X20) magnification. The arrow on the liver tissue indicates comparatively enlarged tissue in the liver. The arrows on the heart tissue shows infiltration of inflammatory cells

4.0. DISCUSSION

MS is a pathologic condition characterized by abdominal obesity, insulin resistance, hypertension, and hyperlipidemia **[1]**. Owing to its regulatory actions through various pathways in insulin sensitivity, hepatic glucose metabolism, diabetic kidney disease, atherosclerosis, cholestatic liver Diseases, FXR may prove to be potential pharmacological target for MS **[13-15]**. The expression of FXR in homogenates of visceral fat is positively associated with the expression of genes involved in insulin signaling and glucose transport (GLUT4, RHOA, ROCK1, and ROCK2), adipogenesis (c/EBPa, PPARg, FABP4, adiponectin, leptin, PPARa, and PLPA2), and inflammation (IL6 and MCP1) **[16]**. Antiparasitic drug IVM is a ligand for nuclear FXR **[5]**. However, IVM has shown antidiabetic activities by reducing blood glucose and cholesterol levels, and also by improving insulin sensitivity in an FXR-dependent manner **[5]**. IVM was also explored in leukaemia, suggesting as chemotherapeutic agent **[17]**. Repurposing of IVM as an inhibitor of the COVID-19 causative virus (SARS-CoV-2) **[18]**. This distinctive pharmacological profile of IVM makes it promising single drug therapy for all the criteria of MS. To develop efficacious drug therapy to combat metabolic syndrome, animal model that mimics all the aspects of human disease is most essential. The major key factor in the progression of MS is obesity leading to all the other alteration in the human body. For induction of model, Olanzapine, via H_1 antagonism plays key role in hyperphagia and increase in body weight by increased expression of the orexigenic neuropeptides, neuropeptide Y and agouti related protein, and decreased expression of the anorexigenic neuropeptide precursor proopiomelanocortin in the arcuate nucleus of the hypothalamus (ARC) leading to antipsychotic-induced hyperphagia and weight gain **[19]**. It was administered weekly for duration of 28 days by intraperitoneal

route. HFHC diet was given during the entire study period of 90 days to the model and treatment group. Recent research has identified primary factors for weight gain and obesity including sedentary lifestyle and overconsumption of calorie dense refined foods. In this model, fat and sugars present in the diet provided more energy than required by the animals. This excess energy is stored in the adipocyte and led to hypertrophy and hyperplasia of adipocytes **[11]**. The model control animals have led to increase in body weight, followed by decrease in the body weight after 10^{th} week (70 days) the possible explanation can be insulin imbalance. Insulin is the prime regulator of carbohydrate, fat, and protein metabolism. It prevents lipolysis of stored fat in the adipose tissue and gluconeogenesis in the liver and stimulates the translocation of the GLUT-4 protein to bring glucose into the muscle cells along with gene expression of proteins essential for the optimal cellular function, cellular repair, and growth, and it shows the metabolic availability of various fuels to the brain **[20]**. Due to excess calorie intake leading to generation of excessive inflammation, the capacity of insulin to orchestrate metabolism becomes compromised. This leads to increase in lipolysis, accumulation of free fatty acids and adipose tissue macrophages accumulation leading to weight loss **[21]** The increase in abdominal circumference of the model control shows visceral adipose tissue, which has a stronger relationship with MS due to its significant secretion of pro-inflammatory **[22]**. High blood pressure is an important constituent of the MS. However, the underlying mechanisms for development of hypertension in the MS are very complicated and remain obscure. Visceral/central obesity, insulin resistance, sympathetic overactivity, oxidative stress, endothelial dysfunction, activated renin-angiotensin system, increased inflammatory mediators, and obstructive sleep apnea have been suggested to be possible factors to develop hypertension in the MS **[23]**. Upsurge in the mean blood pressure was observed in the model control. IVM treatment significantly showed the decrease in the mean blood pressure. MS is often associated with LV diastolic dysfunction **[24]** and higher blood pressure accelerates LV diastolic dysfunction **[25]**. IVM treatment preserved the levels of LVEDP coronary blood flow, $dp/dt_{max,}$ $dp/dt_{min..}$ Reports **[26, 27]** have suggested that FXR plays an important role in glucose metabolism. This occurrence of prevention in rise of glucose level may be since FXR participates in the expression of phosphoenolpyruvate

carboxykinase gene which is rate controlling enzyme of gluconeogenesis **[28]**. HFHC diet shows impairment in glucose tolerance. The oral glucose tolerance test in model control displayed decrease in glucose clearance indicating impaired glucose tolerance. However, treatment with IVM showed significantly higher glucose clearance on 90^{th} day. FXR has reportedly shown decrease in TG levels by increasing clearance of VLDL and chylomicrons by modulating LPL activity **[3]**, inducing PPARα leads to decreases plasma triglyceride levels **[29]** and inhibiting SREBP-1c **[30]**. Treatment with IVM significantly prevented increase in TCHL, TG, LDL, VLDL and prevented decrease of HDL as compared to model control. Fatty liver is closely related to impairment in glucose, fatty acid, and lipoprotein metabolism, and it is now widely recognized as the hepatic manifestation of the MS. Rats given olanzapine and HFHC diet showed significant rise in ALT, AST, ALP and total bilirubin levels showing hepatic injury. Whereas, IVM treated rats attenuated the rise. Oxidative stress, mainly caused by mitochondrial dysfunction, is strongly linked with MS development. Increased oxidative activity that, along with an insufficient antioxidant defense, causes an overproduction of reactive oxygen species in mitochondria, causing damages in other macromolecules such as lipids, proteins and nucleic acids **[22]**. MDA levels were increased in the model control while the treatment group showed decrease in the level compared to the model group. While decrease in the level of GSH, CAT and SOD was observed in the model control group and the treatment group prevented the decline in the levels of antioxidant enzymes. The histopathological study of liver tissue in the model control presented increase in the deposition of the fat in the vacuoles and hence showed vacuoles larger in size and the IVM treated rats showed smaller vacuoles in the liver tissue. The histopathological study of heart in control group showed intact myofibrillar structure with striations and no infiltration whereas, myofibrillar degeneration with infiltration of the inflammatory cells was observed in model control group. IVM treatment showed significantly less infiltration of the inflammatory cells.

5.0. CONCLUSION

In conclusion, the present study revealed that IVM effectively ameliorated the metabolic syndrome by improving the hemodynamic parameters, LV function, insulin resistance, dyslipidemia, hypertension and oxidative stress. These results appeared to be

promising in reducing the mortality caused by metabolic syndrome and developing newer strategies to combat in the era of metabolic diseases.

6.0. REFERENCES

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