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Protective Role of the Farnesoid X Receptor Ligand Ivermectin in Rats with Diabetic Dyslipidemia

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Abstract: Diabetic dyslipidemia describe the pathophysiology surrounding the effects of insulin resistance on abnormal lipid levels which shows increased plasma concentration of triglycerides, reduced concentration of high density lipoprotein cholesterol and a qualitative alteration of low density lipoprotein fraction due to the preponderance of the small and dense LDL. Ligand-activated nuclear receptors provide promising new targets for both glucose and lipid homeostatis. The Farnesoid X receptor is one of the most important member of the nuclear receptor superfamily and expressed in liver, intestine and adipose tissue. FXR indirectly affects Phosphoenolpyruvate carboxykinase and modulating gluconeogenesis. FXR agonists are promising therapeutic agents for treatment of diabetic dyslipidemia. ***Objectives:*** Objective of the present study is to find Protective Role of the Farnesoid X Receptor Ligand Ivermectin in Wistar Rats with Diabetic Dyslipidemia. ***Methods***: Animals were randomly divided into different groups viz. Normal control, Model Disease control; Standard control and Test groups. Animals were induced diabetes with high fructose diet (69 % carbohydrate, 21 % Protein, 10 % Fat). All drugs were administered orally once a day for 28 days at a fixed time. Body weight and food intake were determined. Biochemical parameters like blood glucose level, Total Cholesterol, Triglyceride, LDL, VLDL, Creatinine, Urea and HDL level were determined. And also Antioxidant parameters were evaluated. ***Results:*** At the end of the study, body weight and food intake were determined and found to be satisfactory results. And results were confirmed by significantly ($p<0.05$) increase in the levels of blood glucose, Total Cholesterol, Triglyceride, LDL, VLDL, Creatinine, Urea and decrease in the level of HDL in fructose induced Diabetic dyslipidemic rats compared to vehicle treated animals. Whereas treatment with Ivermectin (0.2, 0.6, 1.8 mg/kg) showed significant ($p<0.05$) decrease in the level of blood glucose, Total Cholesterol, Triglyceride, LDL, VLDL, Creatinine, Urea and increase in the level of HDL in Diabetic dyslipidemic rats. Also Ivermectin exhibited significant ($P<0.05$) reduction in MDA level and enhance activity of SOD and Catalyse level.

Keywords: Ivermectin, Diabetic dyslipidemia, Farnesoid X receptor, Atorvastatin

INTRODUCTION

Diabetic dyslipidemia has been used to describe the pathophysiology surrounding the effects of insulin resistance on abnormal lipid levels which shows increased plasma concentration of triglycerides (TG), reduced concentration of high density lipoprotein cholesterol (HDL-C) and a qualitative alteration of low density lipoprotein (LDL) fraction due to the preponderance of the small and dense LDL (sdLDL).1 According to National Cholesterol Education Panel Guidelines, Diabetes is considered a CHD equivalent.2 Although the first priority of treatment is to decrease LDL-C level it may require an advanced treatment that normalize the lipid profile which minimize the risk of cardiovascular event.3 Ligand-activated nuclear receptors provide promising new targets for both glucose and lipid homeostatis.4 The Farnesoid X receptor (FXR) is

one of the most important member of the nuclear receptor superfamily and expressed in liver, intestine and adipose tissue. FXR is activated by bile acids. After ligand binding, FXR binds to DNA elements which is called as FXR response elements (FXREs).5 On activation of FXR, it regulates bile acid synthesis, conjugation, transportation and other aspects of lipid and glucose metabolism.6 Serum triglyceride level reflect the balance between production and clearance of triglyceride-rich lipoproteins such as very-low-density lipoprotein and chylomicrons. FXR induces the expression of the very-low density lipoprotein receptor.7 FXR regulates the expression of peroxisome proliferator-activated receptor (PPAR)-α.8 FXR down regulates sterol response element-binding proteins (SREBP)-1c expression, which is responsible for decrease in hepatic triglyceride secretion.9 FXR decreases triglyceride levels by: increasing their clearance by modulating LPL activity, inducing PPARα and inhibiting SREBP1c. Activation of FXR cause increase in LDL receptor (LDLR) and scavenger receptor-BI (SR-BI) involved in cholesterol uptake.10, 11 FXR also regulate carbohydrate metabolism. FXR participates in the regulation of the fasting induced gluconeogenic response via induction of the small heterodimer partner (SHP).12 In this way, FXR indirectly affects Phosphoenolpyruvate carboxykinase (PEPCK) and modulating gluconeogenesis.13 FXR activation may improves peripheral insulin sensitivity.14 and promotes glycogen synthesis.15 In view of its central roles in coordinating regulation of both glucose and lipid metabolism, we proposed, FXR agonists are promising therapeutic agents for treatment of diabetic dyslipidemia. On the basis of above, objective of the present study is to find Protective Role of the Farnesoid X Receptor Ligand Ivermectin in Wistar Rats with Diabetic Dyslipidemia.

MATERIAL AND METHODS

Drugs and chemicals

Ivermectin and metformin were obtained from Intracin Pharmaceuticals Pvt Ltd, Nadiyad and Sun Pharmaceutical, Vadodara respectively. Atorvastatin obtained from Cadila Pharmaceuticals Ltd. Ahemdabad. Other chemicals used in this project were of analytical grade and were obtained from Astron Chemicals, Ahmedabad and SD Fine Chemicals, Mumbai, India. All the biochemical tests were performed using the standard reagent kits (GLU 011, TGL 014, CHO 014, HDL 020, CKB 012, and URE 022) purchased from Coral Clinical Systems, Tulip Group, Goa, India.

Animals :

Male Wistar rats weighing 260-280 gm were procured from Zydus Research Center, Ahemdabad. The animals were kept in polypropylene cages (3 in each cage) at an ambient temperature of 25 ± 2° and 55 ± 5 % RH. A 12/12 h light and dark schedule was maintained in the animal house. The rats had free access of water and were fed with commercially available feed (54% carbohydrate, 26% Protein, 3% Fat). The protocol of experiment (APC/IAEC-2013/1322) was approved by Institutional Animal Ethics Committee as per the guideline of the Committee For the Purpose of Control and Supervision of Experiment on Animals (CPCSEA), ministry of Social Justice and Empowerment, Government of India.

Experimental design:

Animals were randomly divided into 6 groups of 6 animal as follows:
Group I: Normal control (NC) (0.5% w/v CMC solution)
Group II: Model Disease control (MC)
Group III: Standard control (STD) (Atorvastatin 10 mg/kg+ Metformin 45mg/kg, p.o.)
Group IV: Test group I (IVM 0.2) (Ivermectin 0.2 mg/kg, p.o.)
Group V: Test group II (IVM 0.6) (Ivermectin 0.6 mg/kg, p.o.)
Group VI: Test group III (IVM 1.8) (Ivermectin 1.8 mg/kg, p.o.)

Group II to VI were induced diabetes with high fructose diet (69 % carbohydrate, 21 % Protein, 10 % Fat). During Experiment Atorvastatin was suspended in 0.5 % w/v CMC. Ivermectin and Metformin were dissolved in distilled water. All drugs were administered orally once a day for 28 days at a fixed time. The body weight of the animals was measured on 1st, 7th, 14th, 21st & 28th day. The food intake of the animals was measured throughout the experiment at 10:00 to 11:00 am. At the end of study the blood samples were collected by retro-orbital plexus. Serum was separated by centrifugation at 3000 rpm for 15 min and used for various biochemical analysis. Oral Glucose Tolerance Test, glucose (GOD/POD method), total cholesterol (CHOD/POD method), total triglycerides (TG) by GPO/PAP method, High density lipoprotein (HDL-C), Low density lipoprotein (LDL-C), Very low density lipoprotein (VLDL) (Freidewald's Formula), creatinine, albumin, urea, and antioxidant; malondialdehyde(MDA), superoxide dismutase (SOD) and catalase (CAT) were determine using UV-Visible spectrophoptometer(UV-1601 Shimadzu, Japan).

Oral Glucose Tolerance Test

Oral glucose tolerance tests (OGTT) was performed on 16 h fasted albino rats using 2 gm glucose/kg body weight fed orally (dissolved in water for injection) through a oral feeding tube. Blood samples were collected from the animals by retro-orbitally at 0, 30, 60, 90 and 120 min after glucose load. Blood glucose levels were measured by GOD/POD

method.

Estimation of Serum Glucose (GOD/POD method): 17
Glucose oxidase (GOD) catalyses the oxidation of glucose to gluconate. The formed hydrogen peroxide (H2O2) is detected by a chromogenic oxygen acceptor, phenol, 4- Aminophenazone (4-AP) in the presence of peroxidase (POD). The intensity of the color formed is proportional to the glucose concentration in the serum.

Estimation of Serum Cholesterol (CHOD-PAP Method):18
Cholesterol esterase are hydrolyses esterified cholesterols to free cholesterol. The free cholesterol is oxidised to form hydrogen peroxide which further reacts with phenol and 4- aminoantipyrine by the catalytic action of peroxidase to form a red coloured quinoneimine dye complex. Intensity of the colour formed is measured at 505 nm and is directly proportional to the amount of cholesterol present in the sample.

Estimation of Serum Triglyceride (GPO/PAP method) 19
Lipoprotein lipase hydrolyses triglycerides to glycerol and free fatty acids. The glycerol formed with ATP in the presence of glycerol kinase forms glycerol 3 phosphate, which is oxidised by the enzyme glycerol phosphate oxidase to form hydrogen peroxide. The hydrogen peroxide further reacts with Phenolic compound and 4-aminoantipyrine by the catalytic action of peroxidase to form a red colored quinoneimine dye complex. Intensity of the colour formed is directly proportional to the amount of triglycerides present in the sample.

Estimation of Serum HDL-Cholesterol 20
Low Density Lipoprotein (LDL) Cholesterol, Very Low Density Lipoproteins (VLDL) Cholesterol and Chylomicron fractions are precipitated by addition of PEG- 6000. After centrifugation, the High Density Lipoprotein (HDL) fraction remains in the supernatant and is determined with CHOD-PAP method.

HDL Cholesterol is estimated in the supernatant by a series of enzymatic reactions which are initiated by the oxidation of Cholesterol to Cholestenone by Cholesterol oxidase, accompanied by the formation of hydrogen peroxide. In a second reaction catalyzed by peroxidase, 4-aminoantipyrine and phenol react with hydrogen peroxide to form red colored quinoneimine. Absorbance at 505 nm is directly proportional to HDL Cholesterol concentration.
Estimation of LDL-Cholesterol 21
After determination of serum cholesterol, TG & HDL-C, serum LDL-C levels were calculated with the help of Freidewald's formula:
Estimation of VLDL levels 21
After determination of serum triglyceride levels, serum VLDL levels were calculated from the equation:

VLDL (mg/dl)= (Serum Triglyceride)/5

Estimation of serum Creatinine 22
Picric acid in an alkaline medium reacts with creatinine to form an orange coloured complex with the alkaline picrate. Intensity of the colour formed during the fixed time is directly proportional to the amount of creatinine present in the sample.
Estimation of Albumin 23
Albumin present in serum binds specifically with bromocresol green at pH 4.1 to form green colored complex, intensity of which can be measured colorimetrically by using 640 nm.
The concentration of albumin in test samples was calculated using following formula.

Estimation of Serum Urea 24
Urease hydrolyzes urea to ammonia and CO2 .The ammonia formed further reacts with a phenolic chromogen and hypochlorite to form a green coloured complex. Intensity of the colour formed is directly proportional to the amount of urea present in the sample. Urease

Estimation of Malondialdehyde (MDA) Level 25
Malondialdehyde (MDA), is an end product of lipid peroxidation process. One mole of MDA Measurement reacts with two molecules of thiobarbituric acid (TBA) under mildly acidic conditions to form a pink coloured chromogen, whose intensity measured at 532 nm.

Estimation of Superoxide Dismutase (SOD) 26
Rate of oxidation of epinephrine & the inhibition of its auto oxidation by SOD was augmented as pH was raised from 7.8-10.2. During oxidation of epinephrine to adrenochrome oxygen was generated by Xanthin oxidase reaction. The auto oxidation of epinephrine proceed by two distinct pathways, only one of which is free radical chain reaction involving O2 & hence inhabitable by SOD.

Estimation of Catalase (CAT) 27
Catalase exerts a dual function. In the ultra-violate range 2 H2O2 shows continues increase in absorbance with decreasing wavelength. The décor position of H2O2 can be followed directly by the decrease in absorbance at 240 nm. The difference in the absorbance per unit time is a measure of the catalase activity.

Statistical analysis:
Result were presented as mean ± SEM. One way analysis of variance (ANOVA) followed by post-hoc dunnett's test was performed for Statistical analysis with $P< 0.05$ set as statistical significance.

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RESULTS

Several diabetic dyslipidemia parameters namely body weight, food intake, oral glucose tolerance test, serum glucose level, lipid profile, creatinine, albumin, urea and antioxidant parameter were measured. Throughtout the study, there was no ststistical significant ($p<0.05$) different in body weight (Table 1) and food intake (Table 2) among the groups.

Table 1 - Effect of Ivermectin on body weight in experimentally induced diabetic dyslipidemia in rats

GROUP	DAY 1	DAY 7	DAY 14	DAY 21	DAY 28
NC	270.0 ± 5.77	281.7 ± 6.00	291.7 ± 3.48	304.0 ± 2.30	314.0 ± 3.21
MC	260.0 ± 5.77	280.0 ± 5.77	292.7 ± 4.63	300.0 ± 5.77	307.0 ± 6.80
STD	266.7 ± 6.67	280.0 ± 5.28	290.0 ± 5.95	296.7 ± 6.91	308.3 ± 8.48
IVM0.2	266.7 ± 6.66	285.0 ± 7.63	292.3 ± 7.68	300.7 ± 6.36	310.7 ± 6.00
IVM0.6	270.0 ± 5.28	286.7± 6.02	297.7 ± 5.44	306.7 ± 7.02	315.3 ± 6.46
IVM1.8	270.0 ± 5.77	285.0 ± 7.63	296.3 ± 8.41	303.3 ± 6.66	317.0 ± 2.64

Values are expressed as mean ± SEM. (N=6).Values are statistically evaluated using ANOVA analysis followed by Dunnett's Post hoc test.

Table 2 - Effect of Ivermectin on food intake in experimentally induced diabetic dyslipidemia in rats

GROUP	Food intake (g)
NC	125.81 ± 0.32
VC	120 ± 0.49
MC	126.4 ± 0.25
STD	121.96 ± 0.49
IVM0.2	119.84 ± 0.84
IVM0.6	120.29 ± 0.37
IVM1.8	120.94 ± 0.54

Values are expressed as mean ± SEM. (N=6).Values are statistically evaluated using ANOVA analysis followed by Dunnett's Post hoc test.

Analysis of oral glucose tolerance pattern during 120mins test period in normal control and model control rats showed statistical significant ($P<0.05$) difference in glucose levels. The glucose level was not found to be decreased in model control rats at 60, 90 and 120 min. However, it was significantly greater than normal control rats. Ivermectin supplemented rats showed lower glucose elevation and faster disposal rates thereby displaying significant improvement ($P<0.05$) in glucose tolerance pattern as compared to model control (Table 3).

Table 3 - Effect of Ivermectin on glucose levels in experimentally induced diabetic dyslipidemia in rats

GROUP	0 min	30 min	60 min	90 min	120 min
NC	5.66 ±0.2022	17.35±0.6918	12.59±0.2000	8.87±0.1281	6.33±0.2100
MC	16.12±0.2725	32.39±0.3572	28.61±0.1902	26.68±0.1682	24.91±0.1948
STD	8.52 ±0.1055	24.32±0.3637	19.30±0.1879	14.39±0.1783	10.57±0.0793
IVM0.2	11.96±0.1902	25.98±0.1545	19.24±0.1791	14.35±0.3566	12.72 ±0.221
IVM0.6	7.637 ±0.032	21.67±0.1281	13.60±0.1264	9.961±0.2210	8.061±0.0550
IVM1.8	11.04±0.1512	27.21±0.3257	19.78±0.4508	15.40±0.1167	13.28±0.1902

Results were presented as mean±SEM, with n=6 animals in each group. One way Analysis of Variance (ANOVA) was used to determine the significant statistical difference between the groups followed by Dunnett's Post-hoc test. $P<0.05$ value was set as the level of statistical significance.

At 28th day serum level of glucose, TC, TG, LDL, VLDL, creatinine, and urea are significantly ($p<0.05$) higher and HDL level is significantly ($p<0.05$) lower in model control group as compare to normal control group. Standard (atorvastatin+ metformin) and Ivermectin (0.2, 0.6, 1.8 mg/kg) treated group shows significantly ($p<0.05$) decreased serum level of glucose, TC, TG, LDL, VLDL, creatinine, and urea and significantly ($p<0.05$) increased level of HDL as compare to model control group. No significant different were noted in serum albumin levels of all groups of animal. Model control animal shows significant ($p<0.05$) increased serum MDA levels and decreased free radical scavenging enzyme (SOD and catalyse) activity in serum compared to normal control group. Standard (atorvastatin+metformin) and Ivermectin (0.2, 0.6, 1.8 mg/kg) treated group shows significant($P<0.05$) reduction

in MDA level and enhance activity of SOD and Catalyse level as compare to model control group (Table 4)

Table 4 - Effect of Ivermectin on biochemical and antioxidant parameter in experimentally induced diabetic dyslipidemia in rats

Parameter	NC	MC	STD	IVM0.2	IVM0.6	IVM1.8
Glucose (mg/dl)	93.87±3.379	288.5±7.07	149.3±6.028	215.1±9.24	131.1±6.277	199±8.28
Total cholesterol (mg/dl)	85.82±1.467	130.1±3.103	89.2±2.766	92.77±5.258	87.14±1.25	93.15±3.209
Triglyceride (mg/dl)	58.68±2.074	138.1±3.808	97.41 ±2.22	104.2±5.908	87.43±3.593	101.8±5.22
LDL (mg/dl)	23.77±1.944	75±3.675	26.8±3.639	31.92±4.046	25.7±5.86	34.42±2.552
VLDL (mg/dl)	11.74±0.414	27.62±0.7616	19.48±0.4445	20.84±0.854	17.49±0.7186	20.36±0.741
HDL (mg/dl)	50.31±0.478	27.52±0.5155	42.92.±2.462	40.7±1.894	43.95±2.264	38.36±1.798
Creatinine (mg/dl)	1.507±0.060	0.5217±0.0502	0.7246±0.028	0.9565±0.03	0.5797±0.049	0.9275±0.03
Urea (mg/dl)	21.55±1.815	51.07±1.967	36.55±0.988	38.33±1.448	36.07±1.988	37.86±1.544
Albumin (g/dl)	3.507±0.081	4.359±0.259	4.121±0.060	4.035±0.126	4.032±0.4309	4.079±0.010
MDA (µg/ml)	1.434±0.05	3.567±0.04	2.362±0.033	2.161±0.045	1.979±0.028	2.407±0.039
SOD (U/min/mg)	10.04±0.263	6.856±0.388	8.773±0.120	7.362±0.290	8.982±0.28	8.656±0.271
CAT (mgof H_2O_2/min/gm of tissue)	5.65±0.157	1.622±0.207	3.742±0.1567	3.041±0.113	4.25±0.226	3.976±0.118

Results were presented as mean±SEM, with n=6 animals in each group. One way Analysis of Variance (ANOVA) was used to determine the significant statistical difference between the groups followed by Dunnett's Post-hoc test. $P<0.05$ value was set as the level of statistical significance.

DISCUSSION

Diabetes and dyslipidemia are associated with a high risk of cardiovascular disease. The most common lipid pattern in people with type 2 diabetes consists of hypertriglyceridemia (hyper-TG), low high density lipoprotein cholesterol (HDL-C), and relatively normal plasma concentrations of low-density lipoprotein cholesterol (LDL-C). The Farnesoid X receptor (FXR) is one of the most important members of the nuclear receptor superfamily.8 On its activation by bile acids, FXR regulates bile acid synthesis, conjugation, and transport, as well as various aspects of lipid and glucose metabolism.9 Thus upon modulation, FXR can be attractive target for diabetic dyslipidemia. Thus this research attempts to evaluate the FXR ligand Ivermectin in diabetic dyslipidemia. Recent evidences tend to identify consumption of carbohydrates more so of refined sugars with high fructose content, as an important culprit in development of hyperglycemia, insulin resistance, hyperinsulinemia, and dyslipidemia, hence a suitable model for evaluating the efficacy of preventive/ameliorating agents. Therefore In current study, fructose diet model was used for induction of diabetes dyslipidemia.28 High dietary fructose intake does not result in a significant weight gain. Supporting evidence, in present study Body weight and food intake was not significantly different between groups.

Diabetes consists of array of dysfunctions characterised by hyperglycaemia hence measurement of blood glucose levels can serve as important tool for diagnosis of diabetes. Ivermectin decrease the blood glucose level in treatment group as compare to model control group. The present study portray prevalence of insulin resistance in fructose fed rats which is clearly indicated by poor the glucose tolerance curve as recorded in oral glucose tolerance test. Ivermectin improve glucose tolerance pattern as compare to model control group. The dyslipidemia accompanying insulin resistance is characterized by distinct changes from a normal plasma lipid and lipoprotein profile. The most commonly observed lipid abnormalities in diabetes are

hypercholesterolemia. A deficiency of insulin is associated with increase in cholesterol levels due to the enhanced mobilization of lipids from the adipose tissue to the plasma.29 The inability of the fat cell to adequately store excess triacylglycerol is a likely first step in the underlying hypertriglyceridemia of insulin resistance.30 Hypertriglyceridemia is a common finding in patients with diabetes mellitus and in insulin resistant states results from accumulation of VLDL particles, either by overproduction, decreased catabolism or both. Increased LDL concentration in the plasma of diabetic rats might be due to the defect in insulin secretion. In particular, many studies have found LDL to be the most dangerous among the plasma lipids, and the oxidation of LDL leads to its increased penetration of arterial walls. 31

In contrast to higher levels of other cholesterol subtypes being a risk factor of dyslipidemia, HDL lower levels are harmful. The decreased plasma HDL level in diabetic rats may be due to the decreased production of HDL by intestine and liver and or due to the glycation of HDL or its apoproteins by high glucose rendering it more pro-atherogenic.30 The present study showed that treatment with Ivermectin significantly decrease the level of TC,TG,LDL,VLDL and significantly increase HDL level. Serum albumin has been suggested to be associated with insulin resistance. Both the antioxidant and anti-inflammatory properties of albumin have been suggested as possible mechanisms for this association.32 In this present study there was no significant change in serum albumin level. In diabetes the delicate filtering system in the kidney becomes gradually destroyed. Urea & creatinine are the parameters to diagnose functioning of the kidney. Changes in serum creatinine concentration more reliably reflect changes in GFR than do changes in serum urea concentrations. Serum concentrations of creatinine depend almost solely upon GFR. Urea formation is influenced by a number of factors such as liver function, protein intake and rate of protein catabolism.33 Ivermectin treatment significantly reduced the serum creatinine and urea levels compared to the model control animals. Hyperglycemia and characteristic dyslipidemia of diabetes mellitus (DM) along with increased oxidative stress leading to endothelial dysfunction have been implicated as early events in the pathogenesis of atherothrombotic macrovascular disease. Oxidative stress results from imbalance between the production of free radicals and antioxidant defense mechanisms and is an important causative factor in several chronic diseases viz diabetes and associated complications. Lipid peroxidation is a marker of cellular oxidative damage initiated by reactive oxygen species. The increased level of lipid peroxidation induces oxidative damage by increasing peroxy radicals and hydroxyl radicals. Malondialdehyde, an end product of lipid peroxidation, is extensively used as a biomarker of lipid peroxidation. 34 Administration of a fructose-rich diet resulted in higher lipid peroxidation by the induction of free radical production in model group as compared to normal animals. A decrease in the rise of MDA level after administration of Ivermectin suggest that Ivermectin decrease the lipid peroxidation. Superoxide dismutase (SOD) converts superoxide to hydrogen peroxide (H2O2) which is then transformed into water. Hydrogen peroxide can also give rise to hydroxyl radicals in the cells. Thus the removal of H2O2 is very important for antioxidant defense in cell or food systems. H2O2 can cross membranes and may oxidize a number of compounds. Glucose oxidation is believed to be a major factor adding to the level of oxidative stress, as glucose is oxidized in a transition-metal dependent reaction to an enediol radical anion that is converted into reactive ketoaldehydes and to superoxide anion radicals. The superoxide anion radicals undergo dismutation to hydrogen peroxide by SOD, which if not degraded by catalase or glutathione peroxidase, and in the presence of transition metals, can lead to production of extremely reactive hydroxyl radicals. 24 Hydrogen peroxide is enzymatically processed by catalase. It was reported that endogenous catalase, antioxidant plays an important role in protecting the kidney from diabetic stress through maintaining peroxisomal and mitochondrial fitness.34 Ivermectin significantly increase the level of SOD and catalyse.

CONCLUSION:

From the above finding, it can be concluded that Ivermectin can be used for management of diabetic dyslipidemia.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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