Resveratrol ameliorates the biochemical changes in fructose induced insulin resistance in rats

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ABSTRACT

There is evidence that high-fructose diet induces insulin resistance, alterations in lipid metabolism, and oxidative stress in rat tissues. The purpose of this study was to evaluate the effect of resveratrol (RSV) administration on biochemical parameters, cytokines, inflammation, oxidative stress, antioxidant status, and lipid metabolism in male rats fed with high fructose diet. Insulin resistance was induced by feeding high fructose diet (60 g/100 g). Forty-five male albino rats were divided into three groups containing 15 rats each. Group I:(Control group) rats received the control diets. Group II (fructose-fed group) rats received fructose- enriched diet (60 g /100g). Group III: (fructose + RSV group) rats received high fructose diet and administered RSV (0.5 mg/Kg body weight /day, intraperitoneally). After 6 and 8weeks of treatment blood samples and liver tissue were collected for determination of serum glucose, insulin, insulin resistance, total cholesterol, triacylglycerols, Adiponectin, tumor necrosis factor- α (TNF- α) and interleukin-6 (IL-6) in addition to antioxidant enzyme (CAT), non-enzymatic antioxidant (GSH), L-Malondialdehyde (L-MDA) and Nuclear Factor kappa B (NF-κB) in liver tissues were also determined. The obtained results revealed that, high fructose diet induce a significant increase in serum glucose, insulin, insulin resistance, cholesterol, triacylglycerols, TNF-α and IL-6 concentrations and decrease in serum adiponectin, with marked reduction in CAT and GSH concentrations in liver tissues and marked increase in L-MDA and NF-kBin liver tissues. Resveratrol treatment to high fructose fed rats reduced the effects of fructose and associated with significant normalization of all serum parameters level and was able to improve dyslipidemia, inflammation and insulin resistance, attenuated the increased L-MDA, enhanced antioxidant status in liver tissues. These results suggest that, Resveratrol is effective in improving the high fructose induced oxidative stress, inflammation and insulin resistance in male rats. Also, the administration of Resveratrol to rats fed a high fructose diet prevents the development of oxidative stress and its associated complications include hyperglycemia, hyperinsulinemia and dyslipidemia.

Key words: Resveratrol, High fructose diet, Insulin resistance, Oxidative stress, inflammatory markers

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1. INTRODUCTION

The increased prevalence of insulin resistance is linked to the western diet and reduced physical activity. These metabolic changes are similar to metabolic syndrome described in humans by Reaven, (1994) and fructose-fed rats are often used to evaluate drugs or treatments of metabolic syndrome. Managing the disorders clustered in this syndrome is of great relevance to prevent and to reduce the risk of all of these pathologies. In animal models, diets high in fructose have specifically been shown to contribute to a metabolic disturbance leading to insulin resistance (Basciano et al., 2005).Obesity and insulin resistance have recently been linked to a low-grade chronic inflammatory response characterized by increased macrophage infiltration, altered cytokine production, and activation of the inflammatory signaling pathway in adipose tissue (Rivera et al., 2009). An excess energy intake leads to obesity and hyperglycemia, which can cause oxidative stress and inflammatory changes (increased levels of tumor necrosis factor [TNF] alpha and interleukin [IL]) (Mazur et al., 2007).These inflammatory changes inhibit insulin signaling and can lead to insulin resistance. Moreover, the inflammatory state induces beta cells dysfunction, which in combination with insulin resistance leads to type2 diabetes (Sjöholm et al., 2006). Thus, pharmacological agents and natural products able

to reduce inflammatory activity possess anti-diabetic properties.

Resveratrol (RSV; trans-3,5,4'-trihydroxystil-bene), a naturally occurring phytoalexin found in juice, peanuts, groundnuts, Itadori tee, grapevines and red wines, has been reported to exert a variety of biological and pharmacological activities, such as anti-carcinogenesis, cardiovascular protection, and anti-inflammatory properties including an inhibitory effect on the production of various cytokines. Some studies have shown resveratrol to protect against the metabolic changes associated with hyper-caloric diets in mice with induced insulin resistance, hyperglycemia, and dyslipidemia (Szkudelska and Szkudelska, 2010).In obese Zucker rats, administration of resveratrol resulted in a significant reduction in triglycerides, free fatty acids, cholesterol and liver triglycerides (Rivera et al., 2009).Apart from natural sources, this compound is recently available in tablets and is recommended as a dietary supplement. In the last years, the interest in resveratrol substantially increased and its broad biological activity at the cellular level has been demonstrated (Bhat et al., 2001).The most recent data indicated that, resveratrol play a crucial role in cardiovascular protection provided by grapes and wines(Bertelli and Das, 2009).Although it is known that, in humans resveratrol is rapidly absorbed after its oral administration and is detected in both plasma and urine, data concerning the potential beneficial effects of the pure compound in humans are still very limited (Bishayee, 2009).However, the most recent data derived from animal studies open a new, promising perspective of the potential use of resveratrol in preventing and/or treating serious metabolic disorders such as obesity and diabetes. Resveratrol has been demonstrated to suppress macrophage activation, which would account for the anti-inflammatory effect of the compound (Tsai et al., 1999).Accordingly, this study was performed to investigate the ameliorative effect of resveratrol on glucose, insulin resistance, Lipid metabolism, biomarkers of oxidative stress, antioxidant status and some inflammatory markers in rats fed high-fructose diet for 8 weeks.

2. MATERIALS AND METHODS

2.1. Experimental animals

Forty-five white male albino rats of 8-10weeks old and weighting 150- 200 gm were used in this study. Rats were housed in separated metal cages and kept at constant environmental and nutritional conditions throughout the period of experiment. The animals were fed on constant ration and water was supplied ad- libitum.

2.2. Chemicals and drugs used

All chemicals were of analytical grade and obtained from standard commercial suppliers. The drug and chemicals used in the present study were:

a. Fructose was obtained as bottle contains (D (+) fructose) 250 g in the crystalline form. It was manufactured by El Nasr Pharmaceutical Company and purchased from El-Gomhouria Co. For Trading Chemicals, Medicines and Medical Appliances, Egypt, Rats fed fructose- enriched diet daily (60 g/100g) for 8 weeks (Rajasekar et al., 2005).

b. Resveratrol (purity ~98%) was obtained as bottle contains 500 mg resveratrol in the crystalline form. Resveratrol manufactured by Alfa Aesar Chemical Co. (St. Louis, Mo, USA) and purchased from Schnelldorf, Germany through the Egyptian International Center for Import Cairo, Egypt. Resveratrol was freshly prepared by dissolving in 5% Ethanol and administered to rats at a dose of (0.5 mg/kg b.wt/ i.p.) daily for 8 weeks (Su et al., 2006).

Insulin resistance was induced in rats by feeding high-fructose diet (60 g/100g of control diet). The diet composition was given in Table 1.

Table (1): Composition of control diet (g/100 g) (National Research Council (1995) :

Ingredients	Control diet	High fructose diet
Fructose	-----	60
soya bean meal (44%C.P. or 49%C.P.)	24	24
ground yellow corn	36.3	36.3
ground whole wheat	22	22
wheat bran	10	10
soya bean oil	3	3
Ca. carbonate	0.5	0.5
salt NaCl	1	1
dry yeast	1	1
Mineral &vit. mixture *	2	2
Methionine	0.2	0.2

*The mineral mix (g/kg) contained 30.5 g $MgSO_4 \cdot 7H_2O$, 65.2 g NaCl, 105.7 g KCl, 200.2 g KH_2PO_4, 3.65 g $MgCO_3$, 38.8 g $Mg(OH)_2 \cdot 3H_2O$, 40.0 g $FeC_6H_5O_7 \cdot 5H_2O$, 512.4 g $CaCO_3$, 0.8 g KI, 0.9 g NaF, 1.4 g CuSO4$\cdot 5H_2O$, 0.4 g $MnSO_4$ andm0.05 g $CONH_3$. One kilogram of vitamin mix contained 3.0 g thiamine mononitrate, 3.0 g riboflavin, 3.5 g pyridoxine HCl, 15 g nicotinamide, 8.0 g d-calcium pantothenat, 1.0 g folic acid, 0.1 g d-biotin, 5 mg cyanocobalamin, 0.6 g vitamin A acetate, 25 g α-tocopherol acetate and 10 g choline chloride

2.3. Experimental design

After acclimatization, the animals were divided into three groups containing 15 rats each, placed in individual cages and classified as follows:
Group I (control group): Rats received control diet, served as control non-treated for all experimental groups.
Group II (fructose-fed group): Rats received fructose-enriched diet (60 g fructose /100g) for 8 week.
Group III (fructose + Resveratrol):
Rats received daily fructose enriched die (60 g fructose /100g of diet) and were administered Resveratrol (0.5 mg/Kg body weight /day, i.p.) for 8 weeks.

2.4. Blood samples

At the end ofweek6 and8th, rats were fasted overnight, Blood samples for serum separation were collected by ocular vein puncture at the end of each experimental period to processed serum that used directly for glucose determination and then kept in a deep freeze at-20° C until used for subsequent biochemical analysis.

2.5. Liver tissue specimens for biochemical analysis

At the end of the each experimental period, rats were sacrificed by cervical decapitation. The liver specimen was quickly removed and weighted, then perfused with cold saline to exclude the blood cells and then blotted on filter paper; and stored at -20°C. Briefly, liver tissues were cut, weighed and minced into small pieces, homogenized with a glass homogenizer in 9 volume of ice-cold 0.05 mM potassium phosphate buffer (pH7.4) to make 10% homogenates. The homogenates were centrifuged at 5,000 r.p.m for 15 minutes at 4°C then the supernatant was used for the determination of catalase (CAT), GSH, L-MDAand NF-κB.

2.6. Tissue specimens (Liver and pancreas) for histopathological examination

Liver and pancreas specimens of rats were carefully examined by naked eyes for detection of any abnormalities. Small specimens were taken from different parts. The specimens were preserved in 10% neutral buffered formalin solution and subjected for histopathological examination according to the technique described by Bancroft and Stevens (1996).

2.7. Biochemical analysis

Serum glucose, insulin, insulin resistance, total cholesterol, triacylglycerols (TG),Adiponectin, Tumor necrosis factor-alpha (TNF-α) and Interleukin-6 (IL-6), liver catalase (CAT), liver GSH, L-Malondialdehyde (L-MDA) and liver NF-κBwere determined using methods described by (Trinder, 1969);BioVendor Rat Insulin (TMB) ELISA Kit, Catalog Number: (RSHAKRIN010TR); (Matthews et al., 1985); (Meiattini et al., 1978); (Bucolo and David, 1973);My BioSource Rat Adiponectin ELISA kit. Catalog Number: (MBS 177263); ALPCO immunoassays TNF-α (Rat) ELISA kit. Catalog Number: (45-TNFRT-E01.1); My BioSource Rat IL-6 ELISA Kit. Catalog Number: (MBS 175908); (Aebi, 1984) and (Fossati et al., 1980); (Moron et al., 1979); (Ohkawa et al., 1979) and My BioSource Rat NF-KB ELISA Kit. Catalog Number: (MBS 2020410).

2.8. Statistical analysis

The obtained data were statistically analyzed by one-way analysis of variance (ANOVA) followed by the Duncan multiple test. All analyses were performed using the statistical package for social science (SPSS, 13.0software, 2009).Values of $P<0.05$ were considered to be significant.

3. RESULTS

3.1. Biochemical results

The obtained data in table (2) revealed a significant increase in serum glucose, insulin, insulin resistance index, T cholesterol and tri-acylglycerols concentrations in rats feeding High-fructose diet all over the periods of the experiments compared to rats fed control diet. Administration of Resveratrol in rats fed high fructose diet resulted in a significant decrease in the concentrations of serum glucose, insulin, insulin resistance index, total cholesterol and triacyl-glycerols all over the experimental periods as compared to untreated fructose fed rats. The obtained data presented in table (3) revealed a significant increase in the concentrations of serum IL-6and TNF-α with significant decrease in Adiponectin concentration in rats feeding High-fructose diet all over the periods of the experiments compared to rats fed control diet. Resveratrol treatment to rats fed high fructose diet resulted in a significant decrease in serumIL-6and TNF-α concentration with a significant increase in serum Adiponectin all over the periods of the experiment as compared to untreated fructose-fed rats.

Table (2): Protective effect of Resveratrol administration on serum Glucose, Insulin, total Cholesterol and Triacylglycerol in high fructose fed rats induced insulin resistance in rats

Parameters	Glucose mg/dl		Insulin (μU/mL)		IR		T. Cholestrol (mg/dl)		Triacylglycerols (mg/dl)	
AnimalGroups	6wks.	8wks	6 wks	8wks.	6wks.	8wks.	6wks.	8wks.	6wks.	8wks.
Control normal	96.69 ± 1.63 ^{c}	98.93 ± 1.35 ^{b}	5.43 ± 0.82 ^{c}	5.52 ± 1.18 ^{c}	1.28 ± 0.19 ^{c}	1.33 ± 0.29 ^{c}	110.93 ± 7.45 ^{b}	113.02 ± 11.41 ^{b}	86.87 ± 2.01 ^{b}	89.69 ± 2.27 ^{bc}
High Fructose	123.20 ± 1.94 ^{a}	134.03 ± 3.19 ^{a}	17.88 ± 1.31 ^{a}	16.97 ± 1.53 ^{a}	5.38 ± 0.39 ^{a}	5.57 ± 0.57 ^{a}	169.04 ± 8.32 ^{a}	170.84 ± 2.94 ^{a}	128.64 ± 12.83 ^{a}	134.53 ± 5.09 ^{a}
High Fructose + Resveratrol	104.16 ± 2.33 ^{bc}	107.52 ± 7.34 ^{b}	6.08 ± 1.29 ^{c}	6.25 ± 0.97 ^{c}	1.55 ± 0.34 ^{c}	1.63 ± 0.28 ^{c}	115.69 ± 14.13 ^{b}	119.40 ± 14.17 ^{b}	105.02 ± 16.53 ^{ab}	102.69 ± 9.10 ^{b}

Data are represented as (Mean±SE), SE: Standard Error, Mean values with different superscript letters in the same column are significantly different at $P \leq 0.05$.

The obtained results in table (4) revealed that a significant decrease in liver tissues catalase and GSH concentrations and significant increase in liver tissues NF-κB and L-malondialdehyde concentration in rats feeding High-fructose diet all over the periods of the experiments when compared to rats fed control diet. Resveratrol administration to rats fed a high fructose diet resulted in a significant increase in liver tissues catalase and GSH activity with significant decrease in liver tissues NF-κB and L-malondialdehyde concentration all over the periods of the experiment as compared to untreated fructose-fed rats.

3.2. Histopathological findings

The examined Liver of control group showing normal histological criteria of blood vessels and hepatic cords (Fig.1). Additionally, Pancreas of control group showing normal histological structures of acini (Fig. 2) and island of Langerhans (Fig. 3).

The examined Liver of rats fed a high fructose diet showing periportal hydropic degeneration of hepatocytes characterized by swollen, pale, vacuolated cytoplasm (Fig. 4), fatty change of the hepatocyes characterized by marked enlargement of the cells by multiple variably sized discrete empty vacuoles (Fig. 5) and lytic necrosis, with loss of cord architecture and replacement of the vacant space by erythrocytes, few inflammatory cells and fibrin threads (Fig.6). Additionally, Pancreas showing degenerated acinar cells with swollen pale vacuolated cytoplasm (Fig.7) and few mitotic figures in some hyperplastic islet cells (Fig. 8). The examined Liver of rats treated with resveratrol fed a high fructose diet showing congestion and dilatation of blood sinusoids with activation of Von Kupffer cells (Fig. 9), small aggregates of inflammatory cells around hyperplastic bile ductules. Mild fatty degeneration of periportal hepatocytes (Fig. 10) and marked vacuolar and hydropic degeneration of acinar cells characterized by swollen pale vacuolated cytoplasm were noticed (Fig. 11). Additionally, Pancreas showing marked hyperplastic proliferation of the functioning cells of the islet of Langerhans (Fig. 12).

Table (3): Protective effect of Resveratrol administration on serumTNF- α, IL-6 and Adiponectin concentrationsin high fructose fed rats induced insulin resistance in rats

Parameters	TNF- α (pg/ml)		IL-6 (pg/ml)		Adiponectin (pg/ml)	
Animal Groups	6 wks.	8 wks.	6 wks.	8 wks.	6 wks.	8wks.
Control Normal	13.80 ± 1.92 ^{d}	16.03 ± 1.30 ^{d}	65.95 ± 10.17 ^{d}	76.90 ± 11.98 ^{cd}	1199.00 ± 94.11 ^{a}	1202.13 ± 69.50 ^{a}
High Fructose	42.30 ± 6.22 ^{a}	44.25 ± 1.56 ^{a}	463.37 ± 51.52 ^{a}	467.99 ± 36.00 ^{a}	485.59 ± 80.89 ^{c}	331.53 ± 23.25 ^{c}
High Fructose + Resveratrol	32.16 ± 1.91 ^{b}	32.91 ± 1.85 ^{b}	304.26 ± 22.40 ^{b}	248.95 ± 49.25 ^{b}	624.83 ± 131.35 ^{cb}	582.96 ± 67.94 ^{b}

Data are represented as (Mean±SE), SE: Standard Error, Mean values with different superscript letters in the same column are significantly different at P ≤ 0.05.

Table (4): Effect of Resveratrol administration on liver CAT activity, GSH, L-MDA and NF-κBconcentrationsin high fructose fed rats induced insulin resistance in rats

Parameters	CAT (mmol/ g. tissue)		GSH (ng/g. tissue)		MDA (Mmol/g. tissue)		NF-Kb (nmol/mL. tissue)	
Animal Groups	6wks.	8wks.	6wks.	8wks.	6wks.	8wks.	6wks.	8wks.
Control Normal	75.45 ± 2.83 ^{a}	76.99 ± 2.77 ^{a}	10.70 ± 1.30 ^{a}	15.74 ± 2.12 ^{a}	26.07 ± 5.92 ^{c}	32.40 ± 4.40 ^{d}	0.33 ± 0.05 ^{c}	0.45 ± 0.03 ^{cd}
High Fructose	19.25 ± 2.94 ^{c}	19.77 ± 3.47 ^{d}	1.61 ± 0.42 ^{c}	1.46 ± 0.29 ^{d}	144.36 ± 11.99 ^{a}	149.30 ± 10.51 ^{a}	1.02 ± 0.05 ^{a}	1.19 ± 0.04 ^{a}
High Fructose + Resveratrol	47.55 ± 5.27 ^{b}	36.19 ± 3.23 ^{c}	3.50 ± 0.90 ^{bc}	3.83 ± 0.69 ^{cd}	107.98 ± 4.07 ^{b}	106.57 ± 8.90 ^{b}	0.73 ± 0.12 ^{b}	0.64 ± 0.10 ^{bc}

Data are represented as (Mean±SE), SE: Standard Error, Mean values with different superscript letters in the same column are significantly different at P ≤ 0.05.

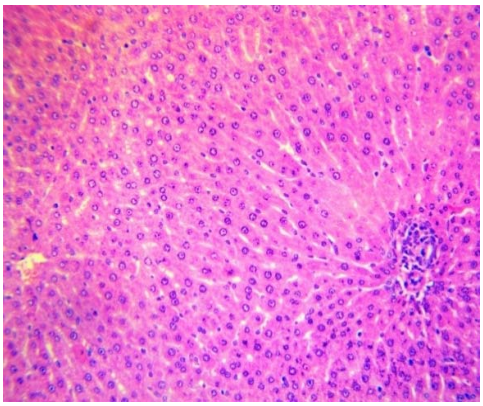

Fig. (1: Liver of control rat, Group I, H&E stain x 200

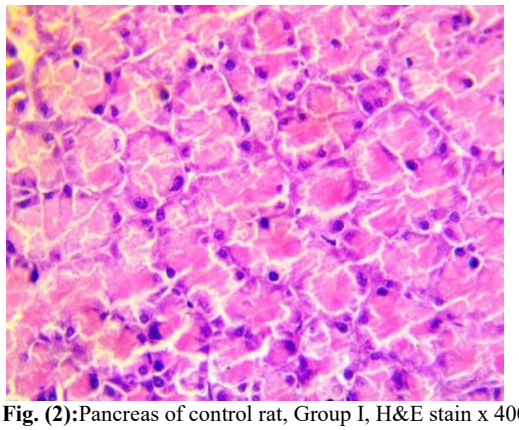

Fig. (2): Pancreas of control rat, Group I, H&E stain x 400

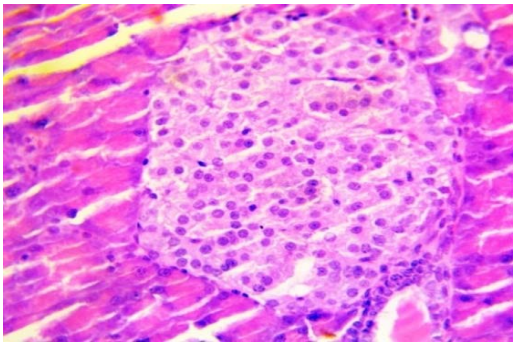

Fig. (3): Pancreas of control rat, Group I, H&E stain x 400

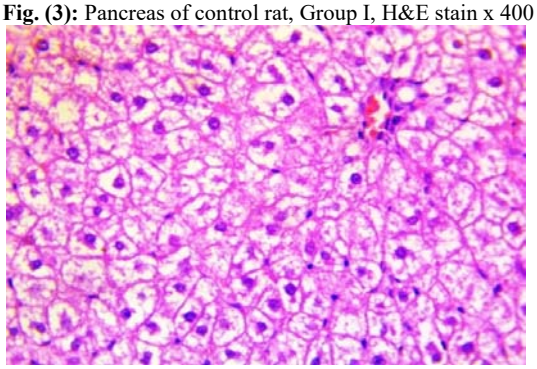

Fig. (4): Liver of rat, Group II, H&E stain x 400

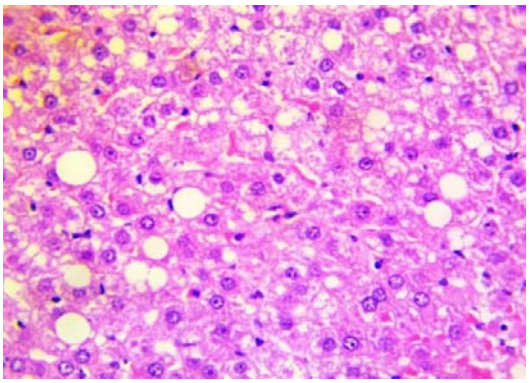

Fig. (5): Liver of rat, Group II, H&E stain x 400

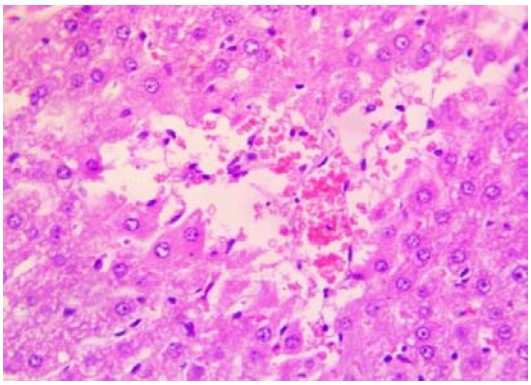

Fig. (6): Liver of rat, Group II, H&E stain x 400

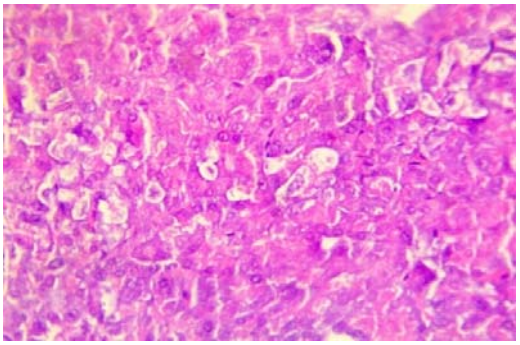

Fig. (7): Pancreas of rat, Group II, H&E stain x 400

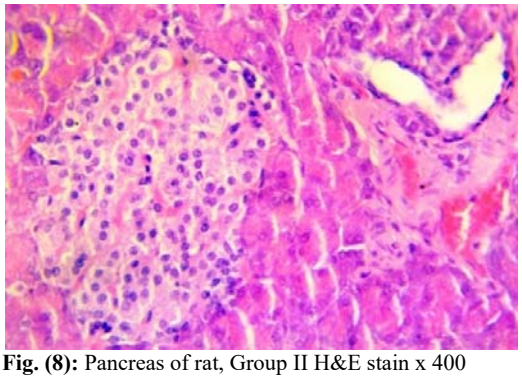

Fig. (8): Pancreas of rat, Group II H&E stain x 400

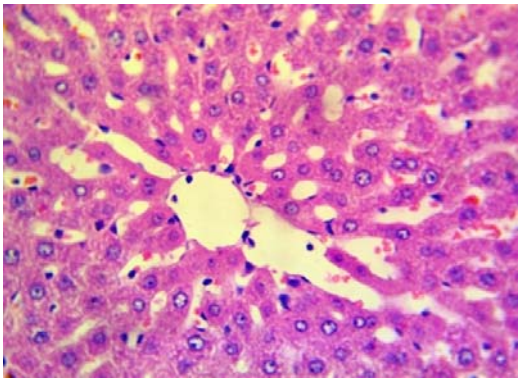

Fig. (9): Liver of rat, Group III, H&E stain x 400

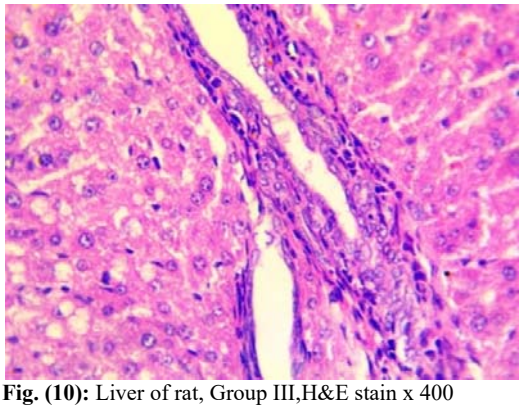

Fig. (10): Liver of rat, Group III,H&E stain x 400

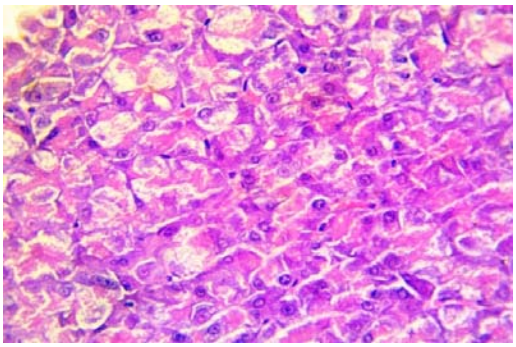

Fig. (11): Pancreas of rat, Group III,H&E stain x 400

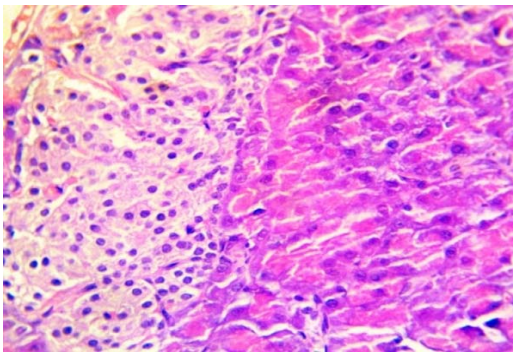

Fig. (12): Pancreas of rat, Group III,H&E stain x 400

4. DISCUSSION

This study focuses on therapeutic intervention that can reduce hyperglycemia as well as metabolic abnormalities with reduction of hepatic oxidative stress in the fructose-fed rats. Fructose is mainly consumed with added sugars. This hexose is essentially metabolized in splanchnic tissues where it is converted into glucose, glycogen, and lactate and to minor extent fatty acids (Tappy et al., 2010).

In this study, we evaluate the effect of resveratrol, a nutritional supplement on insulin resistance, Antioxidant status, Hepatic oxidative stress and inflammation in fructose-fed rats. High fructose intake over a long period is well known risk factor for diabetes and obesity (Basciano et al., 2005). We used a high fructose diet as animal model for the induction of insulin resistance, metabolic syndrome and oxidative stress.

Nakagawa et al., (2006); and Reungiui et al., (2007) have shown that long-term fructose feeding induces diabetes associated with insulin resistance and metabolic syndrome in experimental animals. Other previous studies showed that fructose consumption causes metabolic alterations in liver that leads to abnormalities including oxidative stress(Abdelmalek et al., 2010).

In the present study, fructose rich diet feeding for 8 weeks showed a significant increase in blood glucose levels along with increased serum insulin levels, HOMA-IR, total cholesterol and triglyceride. Administration of resveratrol reduced the increased blood glucose levels, insulin resistance along with serum cholesterol and triglyceride.

Fructose consumption does not directly promote insulin secretion from pancreatic cells due to the low concentrations of the fructose transporter GLUT5 in ß cells (Elliott et al., 2002), but the glucose produced as a result of fructose metabolism stimulates insulin release, and the high fructose diet induced insulin resistance which prevents the insulin from effectively metabolizing glucose. As a result, increased amounts of glucose circulate throughout the body (hyperglycemia). Insulin resistance can also lead to compensatory hyperinsulinemia, where the body attempts to balance the reduced effects of insulin by producing and releasing more insulin (Suga et al., 2000).Insulin resistance may occur due to a defect in insulin binding caused by a decrease in the insulin receptor number or affinity or defects at the level of effectors molecules such as glucose transporters and enzymes involved in glucose metabolism(Kim et al., 2000).Also, resveratrol increases phosphorylation of signaling proteins, including IRS- 1, Akt and PI3K (Hong et al., 2014) increased GLUT4 expression (Chi et al., 2007) and SIRT1 (silent information regulator 1) expression in diabetic rats (Sadi et al., 2014).The SIRT1 is involved with the regulation of inflammation, stress resistance, intracellular metabolism, mitochondrial biogenesis, apoptosis and glucose homeostasis. As confirmed by Cummings et al., (2010) who reported that, the presence of an antioxidant with insulin sensitizing activity ameliorates the effect of fructose by improving glucose homeostasis, which is likely due to preserving B-cell function.

Excess TG with subsequent excess free fatty acids may cause insulin resistance by stimulating gluconeogenesis and activating protein kinase C (PKC) and Jun N-terminal kinase (JNK), which may interfere with tyrosine phosphorylation of insulin receptor substrates (IRS) (Dey et al., 2005).A Key contributor to insulin resistance and the metabolic syndrome appears to be the abundance of TG perhaps in part due to high fructose intake, exceeding the storage capacity of adipose tissue and impairing adipocyte signaling. The end result is ectopic fat storage, accompanied by modified secretion of hormones and cytokines by adipose tissue and an inflammatory state, all of which cause damaging abnormalities in signaling within insulin-sensitive tissues (Basciano et al., 2005).

Nevin et al., (2011) explained that, hypolipidemic effect of RSV due to increase plasma lipid uptake or by decrease fatty acid synthesis. Also, Rivera et al., (2009) stated that, RSV decreases FFA circulating levels, leading to decrease triglyceride and cholesterol production and accumulation in the liver.

In this study serum TNF-α and IL-6 level were significantly higher in fructose fed rats with significant increase in liver NF-κB. Resveratrol administration significantly reduces these parameters. TNF-α accelerates insulin resistance (Liu et al., 2002).Experimental studies have shown that treatment with pro-inflammatory cytokines induces hypertriglyceridemia and insulin resistance. TNF-α down regulates the tyrosine kinase activity of the insulin receptor, thereby increases insulin resistance (Fernández-Veledo et al., 2009).The reduction of inflammation is an important target in the treatment of metabolic syndrome. Phenolic compounds have been shown to inhibit nuclear factor-kappa B (Milne et al., 2007). Additionally, serum Adiponectin was significantly lower in fructose fed rats. Resveratrol administrations significantly increase Adiponnectin. Adiponectin concentrations correlate negatively with glucose, insulin, triglyceride serum levels, liver fat content and body mass index and positively with high-density lipoprotein-cholesterol levels, hepatic insulin sensitivity and insulin stimulated glucose disposal. Adiponectin has been shown to increase insulin sensitivity and decrease plasma glucose by increasing tissue fat oxidation (Nishida et al., 2007). A diponectin is considered to improve insulin sensitivity by up regulating the expression of insulin receptor substrate-1 in skeletal muscles (Kadowaki et al., 2006). RSV has a stimulatory effect on the expression levels (Ajmo et al., 2008) or the secretion (Qiang et al., 2007) of adiponectin. Also, Wang et al., (2011) showed that, RSV plays a positive role in regulating adiponectin expression.

Both experimental and clinical studies indicate that oxidative stress plays a major role in the development and complications of type 2 diabetes (Giacco et al., 2010). Free radicals are generated in diabetes by glucose oxidation. The oxidative stress may be amplified by diabetes-induced metabolic stress, tissue damage, and apoptosis, leading to increased free radical production and compromised free radical scavenger systems, which further exacerbate the oxidative stress. Oxidative stress can also lead to damage of cellular organelles, and development of insulin resistance (Yu et al., 2012). In our study, high fructose feeding increased oxidative stress as evidenced by significant reduction of CAT and GSH levels in the liver in comparison to control group and increase lipid per-oxidation as increase liver L-MDA. Resveratrol increased hepatic CAT and GSH levels and decrease hepatic L-MDA in the fructose-fed liver. This beneficial antioxidant effect might be responsible for improved insulin sensitivity in fructose-fed rats after resveratrol administration. RSV has been shown to increase plasma antioxidant capacity and to decrease lipid per-oxidation (Wenzel et al., 2005).RSV has been shown to scavenge hydroxyl, superoxide, metal-induced radicals (Leonard et al., 2003). Nevertheless, its capacity of inhibiting oxygen free radical formation may come from the inhibition of reactive oxygen species (ROS) production by nicotinamide adenine dinucleotide phosphate (NADPH) oxidases (NOX) (Chow et al., (2007) and by the induction of anti-oxidative enzymes or their substrates, such as catalase(Xia et al., 2010).RSV has the ability to up-regulate the expression of cellular antioxidant and detoxification enzymes to improve cellular resistance to oxidative stress (Buryanovskyy et al., 2004).

5. CONCLUSION

Resveratrol is a food supplement that causes hypoglycemia, hypotriglyceridemia and decreased insulin resistance. It has antioxidant and anti-inflammatory effects. These results support its utilization as a therapeutic tool that targets the hazards of metabolic syndrome. Further researches are needed to clarify the mechanistic role of this supplement in human diabetic patients

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