

The Effect of Resveratrol on Insulin Resistance, Metabolic Syndrome and Hepatic Oxidative Stress in Fructose- Fed Rats

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Keywords

Resveratrol

High fructose diet

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Abstract

Background/Aim: Metabolic syndrome and oxidative stress are common complications of type 2 diabetes mellitus. The aim of this work was to study the effect of resveratrol, a widely used nutritional supplement on insulin sensitivity, some metabolic parameters and hepatic oxidative stress in high fructose- fed rats. **Material & methods:** Male Wister rats (180-200g) were divided into 3 groups 10 per each. G1: Control group was fed 65% corn starch diet. G2: Fructose-fed insulin resistant group (HFD) was fed 65% fructose diet. G3: (HFD + Resveratrol) was fed with 65% fructose along with a single dose of 10 mg/kg/day of resveratrol orally through intra gastric tube for a period of 8 weeks. **Results:** At the end of the feeding schedule, HFD group had significant hyperglycemia, hyperinsulinemia and insulin resistance as evident by HOMA IR. There were significant increase in triglyceride and nitric oxide levels as well as in hepatic ThioBabaturic Acid Reactive Substance (TBARS) and significant decrease in vitamin C in HFD group compared with control group. Administration of resveratrol significantly improved the altered metabolic parameters, hepatic oxidative stress parameters and significantly reduced inflammatory markers (Monocyte Chemoattractant Protein -1(MCP-1), Tumor Necrosis Factor α (TNF α) and Regulated on Activation Normal T cells Expressed and Secreted (RANTES). **Conclusion:** Resveratrol supplementation might attenuate the insulin resistance, hepatic oxidative stress state and inflammatory state in metabolic syndrome.

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INTRODUCTION

Researches in humans and experimental animal models have focused on the association between obesity, insulin resistance, dyslipidemia and hypertension, and have been closely linked to the development of diabetes and cardiovascular disease.¹ Diabetes Mellitus (DM) is a common, serious, chronic, and currently incurable metabolic disorder of worldwide significance. The disease is known to be associated with a high risk of micro vascular and macro vascular complications and very often leads to premature death. Despite the availability of many anti diabetic agents and pharmacotherapies, targeting cardiovascular risk factors, the morbidity, mortality and economic consequences of DM is still a great burden to patients, society, health care systems and the economy².

Many pharmacologic and non-pharmacologic interventions have been developed based on current understanding of the pathophysiology of type 2 diabetes (DM-2). However, the existing treatments have limitations either because of their side effects, particularly weight gain and hypoglycemia or contraindications that limit their use. Furthermore, none of the current therapies have a significant impact on the associated risk factors. Therefore, there is a need , for new therapies that may improve not only hypoglycemic effect but also the

associated problems. Resveratrol (3,5,4'-trihydroxystilbene) belongs to the large group of polyphenols found in different plant species. The richest natural source of resveratrol is *Polygonumcuspidatum* a plant root extract of which have been used in oriental folk medicine. Considerable amounts of resveratrol were also found, among others, in peanuts, groundnuts, Itadori tee, grapevines and red wine^{3,4}. Apart from natural sources, this compound is recently available in tablets and is recommended as a dietary supplement. The interest in resveratrol substantially increased and its broad biological activity at the cellular level has been previously demonstrated. Resveratrol cardio protective effects had been demonstrated before^{5,6}, its beneficial role in cancer^{7,8} and its anti-inflammatory & antioxidant properties⁹. Moreover, resveratrol, as a component of red wine, is thought to be responsible for the French paradox i.e. low mortality due to coronary heart disease as a result of moderate consumption of red wine¹⁰.

Data reinforced this theory and indicated that resveratrol play a crucial role in cardiovascular protection provided by grapes and wines¹¹. 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

limited¹². However, more researches are needed on the anti-diabetic activity of resveratrol along with its diverse biological action that directly or indirectly reduce diabetic complications in fructose fed animals. Consumption of fructose in the form of high fructose corn syrup (HFCS) is increasing every day. Long term fructose intake induces diabetes along with insulin resistance and metabolic syndrome in human as well as experimental animals¹³. The aim of this work is to study the effect of resveratrol, a widely used nutritional supplement on insulin sensitivity, some metabolic parameters, hepatic inflammatory markers and oxidative stress in high fructose-fed rats.

MATERIALS AND METHODS

Experimental animals: All animal experiments were undertaken with the approval of Ethical Animal Research Committee of Tanta University. Thirty male Wister rats weighing (180–200 g) were purchased from the Faculty of Science (Tanta University). The animals were housed at temperature 22 ± 2 °C and 12 h dark/light cycle throughout the study. Animals were randomly divided into three groups 10 per each. G1: Control group was fed 65% corn starch diet, G2: High Fructose-Fed insulin resistant group (**HFD**) was fed 65% fructose diet and G3: (HFD +

Resveratrol) was fed with 65% fructose along with a single dose of 10 mg/kg/day of resveratrol (Sigma) orally through intra gastric tube for a period of 8 weeks.¹⁴ The composition of both diets is determined according to Perter et al.¹⁵

Body weight and food intake: Changes in body weight and food intake patterns of rats in all groups were noted throughout the experimental period. The weight of each rat was recorded on day 0 and at weekly intervals throughout the course of the study. The quantity of food consumed by each group was recorded, to facilitate measures of food intake, rats were housed conventionally in individual stainless steel hanging wire-mesh cages, with food and tap water provided ad libitum. On arrival, all rats were placed immediately into their respective experimental conditions and allowed access to a pre weighted amount of food so that the first intake measures could be obtained the next day¹⁵ and the food consumption per rat was calculated for all groups.

Biochemical assay:

After 8 weeks of feeding and drug administration, rats were fasted overnight, animals were sacrificed by exsanguination. Blood was collected by cardiac puncture, serum was separated by centrifugation at 4000 rpm (4 °C) for 15 min and serum was frozen at -70°C in aliquots until biochemical analysis were performed. **Blood**

glucose was measured using glucometer (Bionime One Touch; Blood Glucose Monitoring System, China)¹⁵.

Serum insulin was measured by using commercially specific ELIZA kit (Mercodia, USA)¹³.

Serum triglycerides: were measured by triglyceride kits (Siemens, India) using an auto blood analyzer (Bayer Corp., USA)¹⁵.

Intraperitoneal glucose tolerance test (IPGTT) was performed according to the method described by Padiya et al.,¹³ Rats from all three groups were injected intraperitoneally with a freshly prepared glucose load of 2 g/kg of body weight. A drop of blood was withdrawn from tail vein by a small puncture using needle to analyze blood glucose using glucometer at (0 min) and at 5, 15, 30, 60 and 120 min after insertion of glucose load.

Nitric oxide (NO) was determined by a commercially available kit (Sigma, USA) according to the method described by Sojitraet al.,¹⁶

ThioBarbituric Acid Reactive Substance (TBARS): Liver tissues were collected and stored at -70 °C for further biochemical evaluation. Each liver tissue was homogenized with 20 times volume of liver weight (100 mg tissue in 2.0 mL buffer) in ice cold 0.05 M potassium phosphate buffer (pH 7.4) and treated separately for different

measurement. Liver homogenate was used for the estimation of ThioBarbituric Acid Reactive Substance (TBARS) a marker of lipid peroxidations¹⁷.

Glutathione measurement: The remaining volume of homogenate was put for centrifugation at 15,000 ×g for 30 min at 4 °C. The supernatant was collected and used for the estimation of reduced glutathione (GSH)¹⁸ as a level of endogenous antioxidant.

Serum vitamin C was measured according to the method described by Roe and Kuether,¹⁹. All of the compounds used for the estimation of different biochemical parameters were obtained from Sigma, USA.

Serum chemokines (MCP -1, TNF α and RANTES) were measured according to the method described by Ilhan et al¹.

Histopathology: liver tissues were fixed in 10% neutral buffered formalin for 48h. The fixed tissue was mounted on the section stage with the appropriate adhesive, 10 μm thin sections were cut on Oscillating Tissue Slicer and then sections were stained with hematoxylin and eosin. Liver specimens were examined blindly by expert pathologists.

Statistical analysis: All values were expressed as mean ± SD. SPSS version 16.0 was used for statistical analysis. Data were statistically analyzed using one-way

ANOVA for multiple group comparison. Significance was set at $p \leq 0.05$.

RESULTS

The average food intake (g/d) and body weight gain:

The average food intake (g/d) showed insignificant variation among the study groups (Fig.1). As regard the body weight gain during the experimental period, there was no significant change after 8 weeks of fructose feeding in HFD group compared with the control group (Fig.2). However,

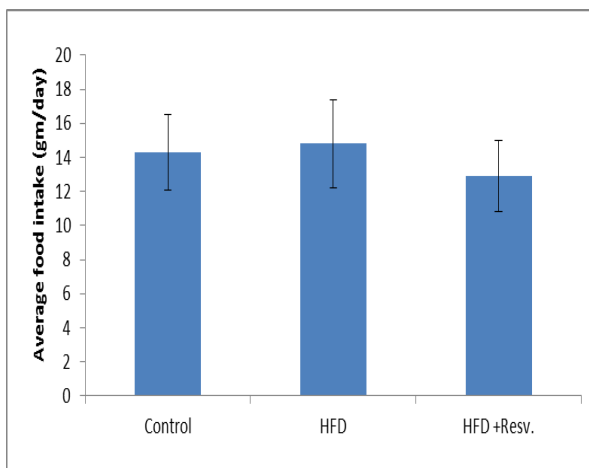


Fig. (1): Average food intake gram/day

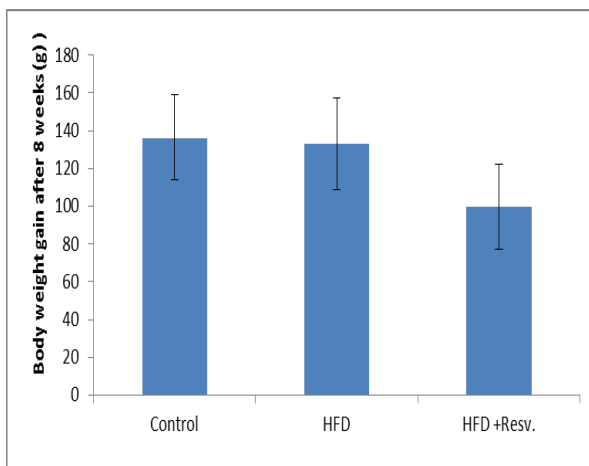


Fig. (2) Body weight gain after 8 weeks

* Means significant change VS. HFD group,

† Means significant change VS. control group

resveratrol administration reduced significantly body weight compared with the control and HFD groups ($P < 0.05$).

Blood glucose levels and intraperitoneal glucose tolerance test (IGTT): After 8 weeks of feeding, rats from HFD group showed a significant increase in blood glucose level compared with the control group ($P < 0.001$). Administration of resveratrol reduced significantly the blood glucose level. There was no significant change between the control and resveratrol administered group. Intraperitoneal glucose load led to marked increase in blood glucose level in HFD group at 5, 15, and 30 minutes compared with the control group. However, resveratrol administration causes insignificant change as compared to 0 basal level (Fig.3)

Serum insulin, HOMA-IR and triglyceride levels: In fructose- fed rats group, hyper insulinaemia was developed. Insulin level was significantly higher in HFD group compared with control group ($P < 0.001$). Resveratrol administration reduced significantly serum insulin level compared with HFD group. There was significant difference between control and resveratrol treated groups ($P < 0.05$) (table1).

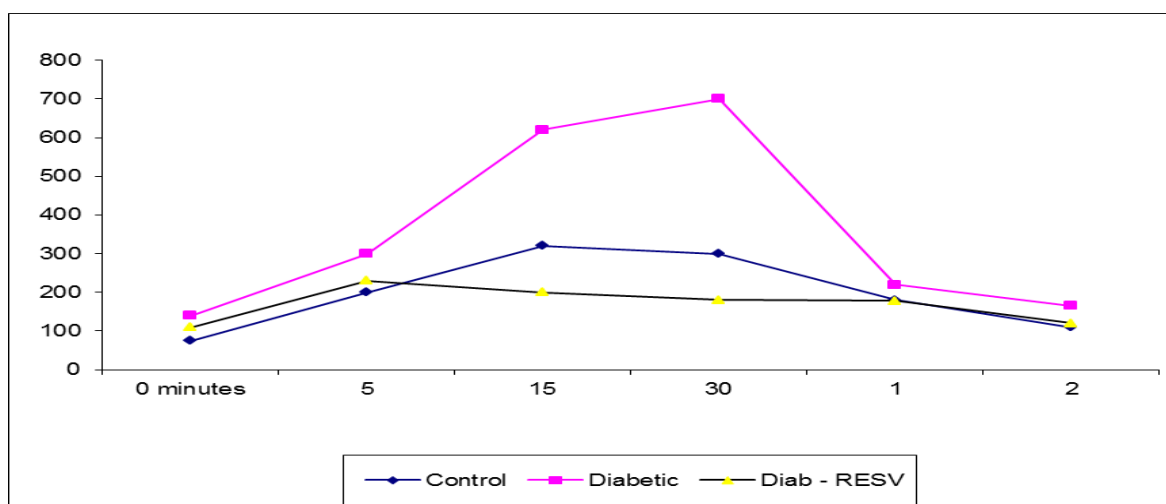


Fig. (3): Effect of resveratrol on intraperitoneal glucose tolerance test

HOMA-IR values were significantly different among the three studied groups. As regard serum triglyceride, HFD group showed significant increase ($P<0.001$) compared with the control group. Resveratrol administration reduced significantly the elevated triglyceride level caused by high fructose diet ($P<0.001$). No significant change was observed between resveratrol treated and control groups.

Serum Nitric Oxide $\mu\text{mol/L}$ (NO): Significant increase in serum nitric oxide was observed in HFD group compared with control group ($P<0.001$). Resveratrol administration reduced NO level significantly ($P<0.001$). Significant change was observed when comparing resveratrol treated and control group ($P<0.05$) (table 2).

Vitamin C (Vit.C) mg/dl: Vitamin C, an important antioxidant to maintain redox balance in different tissues. Vit. C levels were reduced significantly in HFD group

compared with control group ($P<0.001$). However, chronic resveratrol administration significantly increased hepatic vitamin C compared to HFD group ($P<0.001$). Significant change was observed when comparing resveratrol treated and control groups (table 2).

Tab (1): Metabolic parameters characteristics of groups:

	Control group	HFD group	HFD + Resv. group	f. test
Insulin m IU/ml	12.8±6.1	46.7±6.21	22.2±5.2	12.633
Glucose (mg/dl)	76.4±6.1	142±22.7	79.3±10.3	8.336
HOMA-IR	1.57±0.71	6.2 ± 0.81	2.71±0.61	5.336
Triglyceride (mg/dl)	120.8±9.4	203.3±36.7	125.8±11.9	6.366

ThioBabitoric Acid Reactive Substance

TBARS n mol /gm weight tissue: Hepatic TBARS levels were significantly increased in HFD group compared with control group ($P<0.05$). Resveratrol administration showed significant reduction of the increased TBARS levels ($P<0.05$). Significant change

was observed when comparing resveratrol treated group to control group (table 2).

Table (2): Serum nitric oxide ($\mu\text{mol/L}$), vitamin C, and liver reduced GSH and TBARS in all the studied groups

	Control group	HFD group	HFD + Resv. group	f. test
Serum Nitric Oxide ($\mu\text{mol/L}$)	30.9 \pm 4.1	72.8 \pm 11.5	39.2 \pm 4.5	81.793
Vitamin C mg/dl	83.2 \pm 12.1	25.1 \pm 3.6	96.9 \pm 16.1	97.940
TBARS nmol/gm tissue weight	0.20 \pm 0.03	0.29 \pm 0.04	0.19 \pm 0.03	56.945
GSH ug/gm tissue wt	0.20 \pm 0.03	0.28 \pm 0.04	0.30 \pm 0.04	13.137

Hepatic GSH $\mu\text{g/gm. wt. tissue}$: Hepatic GSH level showed no significant change when comparing HFD group to control group. Administration of resveratrol significantly increased hepatic GSH level compared to HFD and control groups ($P<0.001$) (table 2).

Table (3): Serum chemokines levels (MCP-1, RANTES levels divided on 10 and TNF- α).

	Control group	HFD group	HFD + Resv. group	f. test
MCP-1 (pg/ml)	46.2 \pm 4.2	71.1 \pm 3.14	47 \pm 8.9	5.669
RANTES (pg/ml) Divided on 10	74.3 \pm 2.53	176.95 \pm 42.1	83.65 \pm 2.27	15.336
TNF-α (pg/ml)	35.4 \pm 4.62	54.9 \pm 18.1	40 \pm 5.1	6.335

MCP-1, RANTES levels and TNF- α :

Serum level of MCP-1 was significantly higher in HFD group compared with control group ($P<0.001$). Resveratrol administration reduced it significantly ($P<0.001$). No

significant change was observed between resveratrol treated and control group. RANTES level showed significant elevation in HFD group as compared with control group ($P<0.001$) and resveratrol administration reduced the elevated RANTES significantly ($P<0.001$). Significant change was observed when comparing the resveratrol treated and control groups. The same was observed as regard TNF- α as it showed significant increase in HFD group compared with control group ($P<0.05$). Resveratrol administration reduced it significantly ($P<0.05$). Significant change was observed when comparing resveratrol treated group and control group (table 3).

Histopathology:

Liver sections showed normal liver architecture (central vein with endothelial lining, hepatocytes with normal nuclei and sinusoidal spaces with Kupffer cells (K)) in control group (Fig. 4 A&B). While, liver obtained from HFD group showed distended central vein, disarrangement of hepatocytes, some nuclei are pycnotic and there are leucocytic infiltrations into the vein (Fig. 4 C&D). On the other hand, resveratrol treated animals showed normal histology except little dilatation of the central vein and slightly more sinusoidal spaces than control (Fig.4 E&F).

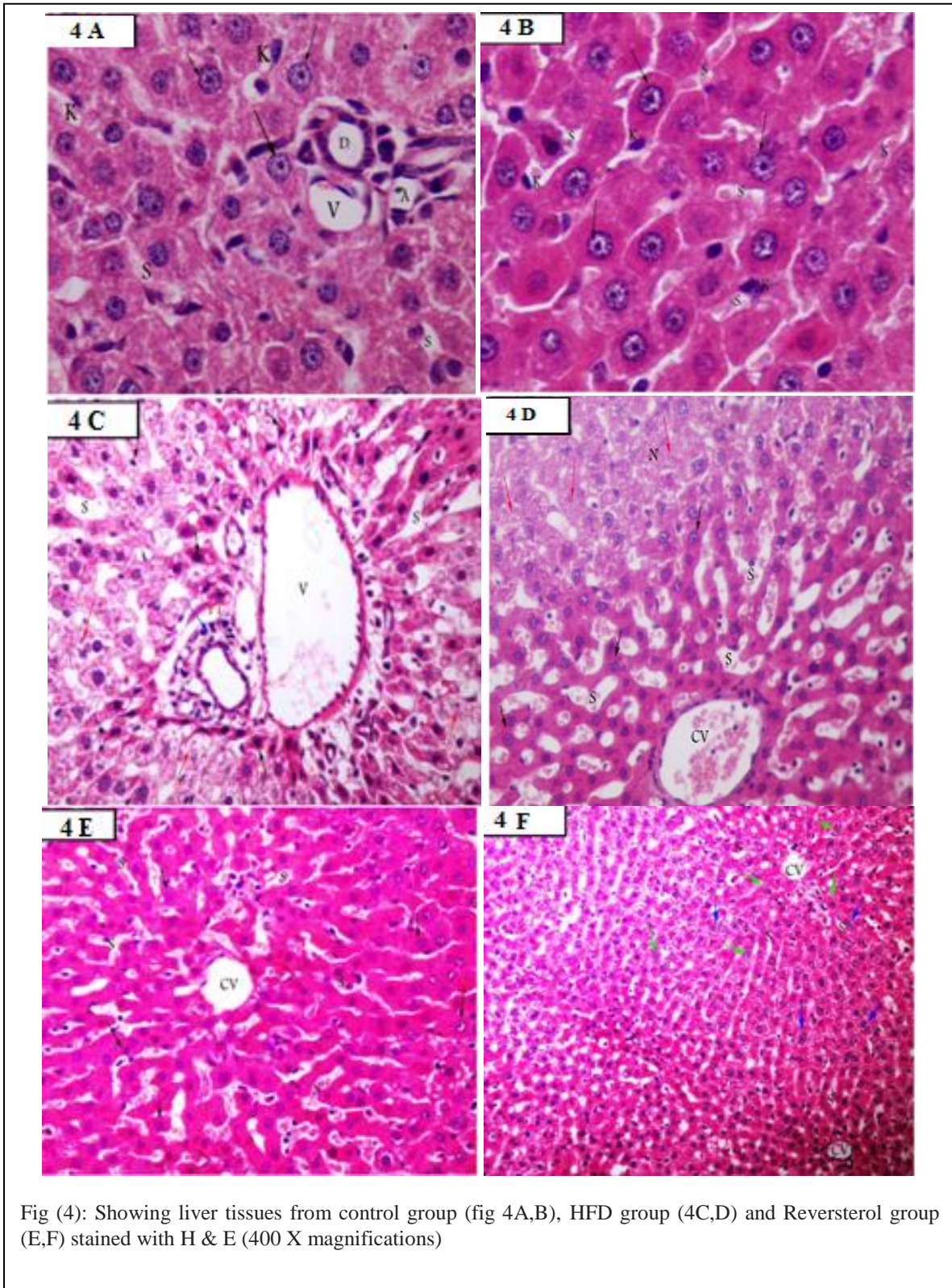


Fig (4): Showing liver tissues from control group (fig 4A,B), HFD group (4C,D) and Reversterol group (E,F) stained with H & E (400 X magnifications)

DISCUSSION

Type 2 diabetes mellitus (DM-2) is a metabolic disorder, influenced by a variety of lifestyle factors including diet, stress, lack of physical activity and alcohol consumption. Current anti diabetic treatment strictly focuses on the management of glycaemia along with reduction of associated diabetic complications including organ damages¹⁴.

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, lactate and to a minor extent fatty acids^{20, 21}.

In this study, we evaluate the effect of resveratrol, a nutritional supplement on insulin resistance and hepatic oxidative stress in fructose-fed rats. High fructose intake over a long period is well known risk factor for diabetes and obesity²². We used a high fructose diet as animal model for the induction of insulin resistance, metabolic syndrome and oxidative stress.

Nakagawa et al²³; and Reungiui et al²⁴ have shown that long-term fructose feeding induces diabetes associated with insulin resistance and metabolic syndrome in experimental animals. ^(23,24) Other previous

studies showed that fructose consumption causes metabolic alterations in liver that leads to abnormalities including oxidative stress²⁵.

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

Laurene et al²⁶ and Chen et al²⁷ had stated that resveratrol administration increased insulin secretion from beta cells and it is possible that higher levels of insulin due to resveratrol might be responsible for improvement of insulin sensitivity.

Although there was no change in body weight gain in fructose-fed animals, resveratrol administration resulted in a significant reduction in body weight gain, which might also responsible for improved insulin sensitivity. Serum triglyceride, which may be also responsible for the increase in insulin resistance in fructose-fed rats was significantly reduced after resveratrol administration.

Increased serum NO levels have been reported in diabetic patients as well as fructose-fed diabetic rats.¹³ Increased NO levels can also induce oxidative damage through the formation of peroxynitrate^{28,29}

In our study, serum NO level was significantly higher in fructose-fed rats compared to the control rats. Administration of resveratrol normalized the NO level in fructose-fed rats. The reduction of serum NO level might be due to reduction of oxidative stress in fructose-fed rats after resveratrol administration²⁸.

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 tissues²².

In this study serum MCP-1, RANTES and TNF- α level were significantly higher in fructose fed rats. Resveratrol administration significantly reduces these parameters. TNF- α accelerates insulin resistance³⁰ 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.³¹The reduction of inflammation is an important target in the treatment of metabolic

syndrome. Resveratrol has been shown to inhibit pro-inflammatory enzymes including cyclooxygenase, lipoxygenase and inducible nitric oxide synthase via activation of peroxisome proliferators-activated receptor gamma. In addition, phenolic compounds have been shown to inhibit phosphoinositide 3-kinases, tyrosine kinases, nuclear factor-kappa B and the expression of endothelin-1.³²

Both experimental and clinical studies indicate that oxidative stress plays a major role in the development and complications of type 2 diabetes³³. 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.³⁴ In our study, high fructose feeding increased oxidative stress as evidenced by significant elevation of TBARS level and reduction of vitamin C levels in the liver in comparison to control group. Resveratrol reduced hepatic TBARS and increased hepatic GSH and vitamin C levels in the fructose-fed liver. This beneficial antioxidant effect might be responsible for improved insulin sensitivity

in fructose-fed rats after resveratrol administration.

Histopathological examination reveals the presence of inflammation, these changes were not observed when fructose-fed rats were treated with resveratrol. Kawasaki et al³⁵ had reported the occurrence of inflammation and fatty liver in fructose feeding rat. Maher et al measured hepatic NRF2 protein level. Nuclear factor E2-related factor 2 (NRF2) is a transcription factor important in the protection against any oxidative stress. During oxidative stress, NRF2 is released from sequestration in the cytoplasm and translocates to the nucleus. NRF2 binds antioxidant response elements (AREs) in the regulatory regions of target genes and activates transcription of several antioxidant enzymes³⁶. Several NRF2 activators have already been developed for treating diseases involving oxidative stress³⁴. Interestingly, NRF2 activators have also been shown to modulate insulin action³⁷. Hyperglycemia-induced endothelial dysfunction, vascular complications and cardiomyocyte damage was prevented by NRF2 activation by reducing oxidative stress. Previous studies demonstrated that beneficial antioxidant effect of resveratrol was associated with increased nuclear translocation of NRF2 in fructose-fed liver. Increased nuclear NRF2 level might have a significant protective role against high fructose induced oxidative stress in liver,

possibly through augmentation of hepatic antioxidant defense enzymes.

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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Competing Interests: None

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المستخلص العربي

هدف الدراسة:

متلازمة التمثيل الغذائي والاكسدة تعد من أهم المضاعفات لمرض النوع الثاني من داء السكري. يهدف هذا الى دراسة تأثير ريسفيراترول وهو مكمل غذائي و يستخدم على نطاق واسع على حساسية الانسولين، وبعض نواحي الأيض و الاكسدة الكبدية في الفئران التي تغذي على تركيز عالي من الفركتوز.

طرق الدراسة:

تم تقسيم الفئران إلى ٣ مجموعات ١٠ في كل مجموعة. المجموعة الأولى (مجموعة التحكم) و تغذى على 65%. نشا الذرة، المجموعة الثانية تغذى على فركتوز عالي التركيز و المجموعة الثالثة تغذى على فركتوز عالي التركيز جنباً إلى جنب مع جرعة واحدة من 10 ملغ /كغ / يوم من ريسفيراترول فمويًا لمدة 8 أسابيع

النتائج

في نهاية الجدول الزمني للتغذية، وجد ارتفاع بمستوى السكر و الأنسولين مع مقاومة الأنسولين مع زيادة كبيرة في الدهون الثلاثية ومستويات أكسيد النتريكو زيادة في كبدي حمض ثيو باربيتيوريك المادة التفاعلية بالكبد وانخفاض كبير في فيتامين سي في المجموعة الثانية مقارنة مع مجموعة التحكم . مع إعطاء ريسفيراترول لوحظ تحسن معلمات الأيض كما أظهرت تأثير ريسفيراترول في تهدئة معلمات الاكسدة مثل البروتين الجاذب الكيميائي ١ ورم نخر ومنظم تنشيط خلايا T العادية .

الخلاصة: إن نتائج الدراسة الحالية تشير بقوة إلى أن مكملات ريسفيراترول يمكن أن تستخدم كأداة علاجية للحد من مخاطر متلازمة الأيض.