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Original Article

Troxerutin Chronic Treatment Protects against Fructose-induced Metabolic Syndrome in Male Rats

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A B S T R A C T

Background and Aims: Metabolic syndrome, a common metabolic disorder, for the serious health consequences such as insulin resistance and lipid abnormalities has been considered as a major clinical challenge with obscure causes. Oxidative stress is an important component of metabolic syndrome, contributing in its development. Troxerutin, a semi-synthetic derivative of natural bioflavonoid rutin, exerts various pharmacological activities, which among all, strong anti-oxidative property is of great importance. The aim of the current study was to evaluate the effects of troxerutin on metabolic parameters and oxidative stress in metabolic syndrome induced by fructose in male rats.

Materials and Methods: In order to induce metabolic syndrome, animals received the water containing 20% fructose for 8 weeks. Troxerutin was administered to animals with the dose of 150 mg/kg orally for 4 weeks after induction of metabolic syndrome following biochemical analysis and oxidative stress marker assessment.

Results: Data showed that high-fructose diet leads to elevation of blood glucose and insulin resistance and causes abnormalities in lipid profile as well as oxidative stress enhancement (signs of a metabolic syndrome) ($p<0.001$). Troxerutin administration improved the detrimental effects of metabolic syndrome on biochemical factors and diminished oxidative stress ($p<0.001$).

Conclusions: Troxerutin administration reverses the deleterious effect of metabolic syndrome in rats with high-fructose diet.

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Introduction

Metabolic syndrome (MS), a constellation of conditions and metabolic irregularities, is a common health challenge worldwide with the characterization of visceral obesity, hypertension, hyperglycemia and dyslipidaemia (increased low-density lipoprotein (LDL) particles and triglyceride-rich lipoproteins as well as decreased high-density lipoprotein (HDL)), which enhances the individual risk for development of type 2 diabetes, cardiovascular events and atherogenesis [1-3]. MS is the result of increasing the obesity prevalence due to sedentary lifestyle and Western type diet and several factors play a role in its pathophysiology such as insulin resistance, chronic inflammation, perturbations in cell signaling and ectopic fat accumulation [4-6]. A new insight into the MS pathophysiology points to the role of oxidative stress and contribution of reactive oxygen species (ROS) overproduction, which induces insulin resistance and exerts key function in MS through salt-sensitive hypertension induction, affecting mineralocorticoid receptors as well as sympathetic excitation in brain [7-10]. Several studies showed that MS induced by high-fat, high-refined sugar diet is accompanied by oxidative stress and nitric oxide synthase dysregulation [11]. Troxerutin (vitamin P4, a derivative of rutin with more hydroxyl groups), a pharmacologically active flavonoid, has been studied for its protective properties in chronic venous insufficiency disease, neural disorders, diabetes and inflammation [12-14]. Studies showed that supplementation with rutin is capable for attenuation of metabolic changes and cardiovascular remodeling in rats under high-carbohydrate and high-fat diet, suggesting a non-nutritive effect of rutin in metabolic syndrome chronic changes [15]. Recent investigations report the ability of cell protection for troxerutin, which is mediated via radical scavenging mechanism and inhibition of oxidative stress-induced cell death [16]. Data demonstrated that troxerutin has a regulatory role in lipid metabolism. Geetha et al., (2014) showed that this derivative suppresses lipid abnormalities in the heart of mice, which were fed with high-fat–high-fructose diet [12]. Troxerutin has the capability to inhibit obesity, hyperglycemia and hyperlipidemia normalization in high-cholesterol diet-induced diabetic animals and protects against atherosclerosis through plasma lipid reduction and homocysteine levels [17-19]. Several mechanisms have been proposed for the protective effects of troxerutin, including a decrease in advanced glycation end products, protein carbonyl levels and reactive oxygen species and enhancement phosphoinositide 3-kinase/Akt activation [18]. The formation of advanced glycation end products, which trigger oxidative stress and contribute in early phases of age-related disorders such as diabetes is inhibited by troxerutin [20, 21]. Data reported that troxerutin could diminish high-fat diet-induced enhancement of hepatic gluconeogenesis by its inhibitory role for endoplasmic reticulum stress-mediated nucleotide oligomerization

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domain activation and the consequent inflammation [22]. Moreover, troxerutin promotes insulin sensitivity, possibly via modifying peroxisome proliferator-activated receptors [23]. Considering the seriousness and prevalence of MS finding new therapeutic strategy to encounter this common problem in modern society and a method for metabolic dysregulation reversal are of great importance, so in this study, we investigated the protective effects of troxerutin on lipids profile and oxidative stress in male MS rats.

Materials and Methods

Subjects

32 male Wistar rats weighing 200-250 g were used throughout this study (from animal house of Rafsanjan University of Medical Sciences). Rats were housed in polycarbonate and standard cages in a temperature-controlled room (22±2◦C, 12 hour light/12 hour dark cycle) with free access to laboratory pellet chow and water. All experiments were conducted between 10:00 A.M to 14:00 P.M and were carried out in accordance with Rafsanjan University of Medical Sciences guidelines for animal care and use with minimizing the number of animals as well as animals' discomfort such as immediate euthanasia after experimental procedures. The groups consisted of 8 rats and each animal was used only once.

Experimental design and induction of metabolic syndrome

Animals were randomly divided into four groups: control (C), control animals, which were treated with troxerutin (C+TXR), metabolic syndrome induced animals (MS) and MS animals, which were treated with troxerutin (MS+TXR). Animals received water containing 20% fructose (purchased from Sigma, USA) for 8 continual weeks in order to induce metabolic syndrome, but the control animals received tap water only. The weight of the animal was measured using a digital scale (FEW, Japan) for body mass index calculation. To measure biochemical parameters, including triglycerides, fasting blood glucose, total cholesterol (TC), HDL and LDL the blood samples were taken after 12 hours fasting with retro-orbital sampling. Troxerutin (purchased from Sigma, USA) was prepared in distilled water and administered orally for 4 weeks with the dose of 150 mg/kg after induction of MS [22-24].

Biochemical assessment, insulin resistance and oxidative stress evaluation

Blood samples were obtained through penetrating the retro-orbital plexus with a capillary tube. The samples were centrifuged at 1000×g for 10 min. to separate the serum and then stored at −20°C until the assay. Quantitative detection of HDL, LDL, TC and triglycerides and the blood glucose was performed by relevant kits (Pars Azmoun, Iran) and expressed as mg/dl. The markers of oxidative stress, including malondialdehyde serum level (µM), total antioxidant activity (mM), glutathione peroxidase, catalase and superoxide dismutase enzyme activities (U/ml) were measured using specific kits (Zelbio, Germany) based on manufacturer procedures. After determining the appropriate amount of insulin to the appropriate kit (Mercodia,

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Sweden) the Homeostatic Model Assessment (HOMA) was used for insulin resistance assessment [25-27]. Homeostatic Model Assessment has been widely used as an insulin resistance index in the clinical or epidemiological studies based on following formula: fasting insulin (micro U/L) x fasting glucose (nmol/L) /22.5 [27].

Statistical analysis

Data are expressed as mean±standard deviation. The one-way analysis of variance (ANOVA) followed by Tukey multiple comparisons was used to analyze the data of body mass index, biochemical and oxidative stress assessment. The computations were done by SPSS software package (version 16) and Excel (Microsoft Excel, 2010, Microsoft Corporation, USA). P<0.05 was considered as the significance level between the groups.

Results

Troxerutin attenuates blood glucose and insulin resistance in metabolic syndrome-induced animals

Table 1 illustrated that blood glucose and insulin resistance in the animals with metabolic syndrome increases in comparison with control (p<0.001). Troxerutin administration with the dose of 150 mg/kg did not alter the abovementioned parameters in the control group (p>0.05) but this dose could decrease the blood glucose and insulin resistance in metabolic syndrome-induced animals in troxerutin treatment in comparison with control group (p<0.001 and p<0.01 respectively) and metabolic syndrome group (p<0.001).

Lipid profile and body mass index alterations in animals under troxerutin treatment

Induction of metabolic syndrome by fructose resulted in a significant elevation in the body mass index, LDL, triglyceride and TC in comparison with control, but the HDL level revealed a reduction (all p<0.001) as shown in Table 2. Troxerutin (150 mg/kg) administration did not alter these factors in the control group (p>0.05), but significantly reduced all parameters compared to metabolic syndrome group (p<0.001) and led to an enhancement in HDL cholesterol (p<0.01).

Table 1. Troxerutin effects on blood glucose and insulin resistance

Variables	C	C+TXR	MS	MS+TXR
Fasting blood glucose (mg/dl)	79.87±5.05	79±4.34	138.12±6.85***	108.62±7.89***,###
Insulin resistance	0.39±0.11	0.37±0.10	1.20±0.22***	0.66±0.17**,###

Data are expressed as mean±SD. Each group consists of 8 animals. *** p<0.001 and ** p <0.01 compared to control group. ### p<0.001 compared to the metabolic syndrome group.
C= control group; C+TXR= control group treated with troxerutin; MS= metabolic syndrome group; MS+TXR= metabolic syndrome treated with troxerutin

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Table 2. Troxerutin effect on the lipid profile and body mass index

Variables	C	C+TXR	MS	MS+TXR
Body mass index (Kg/m2)	7.29±0.53	7.02±0.43	9.34±0.45***	7.44±0.32###
High-density lipoprotein (mg/dl)	45.87±4.96	46.5±2.44	32.75±1.98***	37.37±2.13***,##
Low-density lipoprotein (mg/dl)	23.87±9.23	24.12±4.41	48.57±5.78***	31.02±4.19###
Triglyceride (mg/dl)	82.5±4.03	83.75±3.84	116.5±9.85***	98±8.65###
Total cholesterol (mg/dl)	86.25±5.06	87.37±2.66	104.12±5.66***	88±2.66###

Data are expressed as mean±SD. Each group consists of 8 animals. *** p<0.001 compared to the control group. ### p<0.001 and ## p<0.01 compared to the metabolic syndrome group.
C= control group; C+TXR= control group treated with troxerutin; MS= metabolic syndrome group; MS+TXR= metabolic syndrome treated with troxerutin

Troxerutin effects on oxidative stress indices

To investigate the role of troxerutin on oxidative stress due to metabolic syndrome induction, it was determined the total antioxidant capacity and malondialdehyde content as well as catalase, superoxide dismutase and glutathione peroxidase activities. Data showed a rise in malondialdehyde content besides a reduction in total antioxidant capacity and enzyme activities (catalase, superoxide dismutase and glutathione peroxidase) compared to the control animals (all p<0.001). Treatment with troxerutin (150 mg/kg) did not affect these indices in the control group (p>0.05), but significantly decreased malondialdehyde and led to the increase in total antioxidant capacity and glutathione peroxidase, superoxide dismutase and catalase activities in comparison with the metabolic syndrome group (all p<0.001) (Table 3).

Table 3. Troxerutin effects on oxidative stress indices

Variables	C	C+TXR	MS	MS+TXR
Antioxidant capacity (mM)	0.91±0.10	0.94±0.11	0.30±0.041***	0.82±0.16###
Malondialdehyde (Mμ)	0.98±0.11	0.95±0.08	2.75±0.43***	1.19±0.35###
Catalase (U/ml)	12.72±2.37	12.96±2.14	5.34±1.081***	10.31±2.83###
Superoxid dismutase (U/ml)	33.78±3.81	35.58±2.83	23.27±4.67***	33.48±2.96###
Glutathion peroxidase (U/ml)	192.20±28.65	193.02±33.13	73.83±18.81***	191.37±53.90###

Data are expressed as mean±SD. Each group consists of 8 animals. *** p<0.001 compared to the control group. ### p<0.001 compared to the metabolic syndrome group.
C= control group; C+TXR= control group treated with troxerutin; MS= metabolic syndrome; MS+TXR= metabolic syndrome treated with troxerutin.

Discussion

Our results showed that long-term fructose diet (in drinking water, 20%) induces MS in rats, which is accompanied by enhanced body mass index and blood glucose, insulin resistance,

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lipid profile abnormalities (increase in LDL, TC and triglycerides levels and decrease in HDL content) as well as oxidative stress dysregulation (decrease in total antioxidant capacity, lower enzyme activity of catalase, superoxide dismutase and glutathione peroxidase and elevated malondialdehyde serum level). Chronic treatment with troxerutin for one month exerted protection and significantly reversed the disadvantageous effects of MS. Blood glucose was diminished and insulin resistance was blocked following troxerutin administration. Moreover, lipid profile and oxidative stress markers were regulated and balanced after 4 weeks treatment with troxerutin. Metabolic syndrome, previously known as syndrome X, is on the rise due to the increased incidence of obesity manifesting raised fasting glucose (>110 mg/dl) or blood pressure (≥130/85 mmHg), dyslipidemia (such as low HDL cholesterol (women <50 mg/dl and men <40 mg/dl) or hypertriglyceridemia (≥150 mg/dl)) and a hallmark of insulin resistance, which leads towards cardiovascular diseases, diabetes mellitus and chronic kidney diseases [28, 29]. In order to study the pathophysiology of MS and finding new drugs, different animal models have been used for induction of MS such as high-fat/sugar diet or transgenic models (overexpressing the enzyme 11β hydroxysteroid dehydrogenase type 1), in this study, we added fructose 20% to the animal's water for 8 weeks, which is considered as a standard and valid method [5, 30-32] and key features of MS (body mass index (BMI) and blood biochemical alteration and insulin resistance) were significantly observed. In metabolic syndrome, there is a dysregulation in adipokines (leptin, adiponectin, apelin) action and secretion and adipocytes show significant changes and glucose homeostasis has been affected [33, 34]. Obesity- initiated MS exhibit a complex linkage with inflammatory responses and inflammation causes metabolic dysregulation through several molecular signaling pathways and anti-inflammatory agents are considered as therapy in this proinflammatory state [35-37]. Moreover, the role of oxidative stress has been explored in MS development. Data indicated a poor antioxidants status in MS subjects with an increased oxidative stress, which is positively correlated with insulin resistance [38]. In regard to Furukawa et al., hypothesis increased NADPH oxidase as well as decreased antioxidant enzymes in accumulated fat resulted from obesity not only leads to a dysregulation in adipocytokines locally but also leads to other organ oxidative stress and eventually diabetes, insulin resistance and atherosclerosis (signs of MS) [39]. Devaraj et al. (2008) reported that fatty meal consumption leads to postprandial oxidative stress in MS [40]. In line with previous reports, our data on oxidative stress biomarkers (decrease total antioxidant capacity and enzyme activity of catalase, superoxide dismutase and glutathione peroxidase and increased malondialdehyde serum level) demonstrated that oxidative stress is a pivotal component of MS.

A number of studies showed that oxidative stress along with chronic inflammation leads

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to the development of metabolic diseases and enhanced systemic oxidative stress is associated with metabolic syndrome. There is a positive correlation between oxidative stress presence and increased LDL and low levels of HDL. Studies indicated that oxidative stress in metabolic disorders may lead to different pathologies such as diabetes [41, 42]. This study showed that fructose administration to animals leads to oxidative imbalance and it was aimed to examine whether troxerutin is able to re-establish the oxidative balance and to prevent oxidative stress. Troxerutin, trihydroxyethylated derivative of the natural bio-flavonoid rutin ($C_{33}H_{42}O_{19}$), is considered as a fascinating target for disease prevention and therapy for its multiple pharmacological effects and anti-inflammatory, anti-oxidative, anti-thrombotic, anti-neoplastic, hepatoprotective, antihyperlipidemic, nephroprotective, cardioprotective and neuroprotective properties have been reported [17, 43-48]. Safety profile and tolerability of troxerutin have been investigated in pre-clinical or clinical studies and no serious adverse reactions were observed even at high doses [49]. Troxerutin administration exerted anti-diabetic effects in high fat and sucrose-induced type 2 diabetes mellitus in rats or high cholesterol-induced insulin resistance in mice and type 2 diabetic patients with different mechanisms, including blood glucose or glycosylated hemoglobin reduction, normalizing serum insulin and lipid profile, improving the insulin signaling molecules, affecting glucose transporter4 proteins and regulating skeletal muscle glucose utilization [14, 24, 50]. Lu et al. showed troxerutin neuroprotection against high-cholesterol-induced cognitive deficits (through blocking the endoplasmic reticulum stress pathways and activating the PI3K/Akt/CREB pathway in brain) and suggested that troxerutin may be a possible candidate for the cognitive deficits therapy in Alzheimer's disease and type 2 diabetes [18]. Geetha et al. (2014) showed that troxerutin blocks lipid abnormalities in the heart of high-fat/high-fructose diet-fed mice [12]. There is not enough evidence in the literature review elucidating the possible protective effects of troxerutin on MS; our study was designed to address this issue in a rat model. Studies indicated that troxerutin displays reversal effects on insulin resistance, lipid accumulation, oxidative damage and hypertension as well as decreasing reactive oxygen species and apoptosis [12, 18]. The results obtained in our study reported that troxerutin treatment improves BMI, blood glucose, insulin resistance, lipid profile and oxidative stress indices to normal or near normal levels in MS, but does not affect these parameters in healthy animals.

Data demonstrated that troxerutin exerts significant therapeutic potential against liver cancer via modulating the liver function enzymes, oxidative damage, xenobiotic enzymes, blocking cell proliferation, inflammatory response suppression and apoptosis induction [51]. Studies suggested that troxerutin can serve as a novel agent for colon cancer chemoprevention via modulating lipid peroxidation and antioxidant status. Troxerutin can act as a free radical quencher and a growth inhibitor [52].

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Conclusion

It is concluded from this study that troxerutin may play a therapeutic role in metabolic syndrome via modulating the insulin resistance, blood biochemical and oxidative stress parameters.

Conflict of Interest

The authors declared that there is no conflict of interest.

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