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Pterostilbene ameliorates insulin sensitivity, glycemic control and oxidative stress in fructose-fed diabetic rats

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ABSTRACT

Aims: The present investigation was designed to explore the effectiveness of pterostilbene (PT) on insulin resistance, metabolic syndrome and oxidative stress in fructose-fed insulin resistant rats.

Main methods: Age-matched, male Sprague-Dawley rats (330 ± 30 g body weight) were allocated into five groups ($n = 10$). Control (C) group received 65% cornstarch, and the diabetic (D) group received 65% fructose for eight weeks. The third group (D + PT20) received 65% fructose and PT 20 mg/kg/day for eight weeks. The fourth group (D + PT40) received 65% fructose and PT 40 mg/kg/day for eight weeks. The fifth group (D + M) received 65% fructose and metformin (M) 100 mg/kg/day for eight weeks. PT was dissolved in 10% β-cyclodextrin and given orally to rats. Several biochemical parameters were determined to assess the PT efficacy against insulin resistance, metabolic complications, and hepatic oxidative stress.

Key findings: Significantly high HOMA-IR ($p < 0.001$) values in D group compared to C group indicate the presence of insulin resistance. Significantly high levels of TBARS ($p < 0.001$) and decreased levels of SOD ($p < 0.001$) and GSH ($p < 0.001$) in hepatic tissues of D group indicate oxidative stress associated with insulin resistance. Pterostilbene treatment to fructose-fed diabetic rats significantly decreased HOMA-IR ($p < 0.001$) values. Furthermore, PT treatment significantly decreased hepatic TBARS ($p < 0.001$) and increased SOD ($p < 0.001$) and GSH ($p < 0.001$) levels in fructose-fed diabetic rats.

Significance: Current study reveals that PT is successful in ameliorating glycemic control, insulin sensitivity while diminishing metabolic disturbances and hepatic oxidative stress in a fructose-induced T2DM rat model.

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1. Introduction

Type 2 diabetes mellitus (T2DM) is mainly typified by impaired glycemic control that results from insulin resistance or insulin deficiency [1]. Around 90% of the diabetic population comprises T2DM; this disease is called "the silent killer", owing to the presence of metabolic complications and comorbidities [2]. Nowadays, a variety of lifestyle factors, such as physical inactivity, alcohol consumption, smoking and dietary habits are the prime risk factors contributing to the progression of T2DM [3]. In recent years, the consumption of fructose in the form of high fructose corn syrup (a popular food sweetener) has been high in many countries, with an increase in consumption of around 1000% [4]. It has been demonstrated that chronic consumption of a 60% fructose diet induces insulin resistance and hyperlipidemia in rats, mimicking the pathology of clinical T2DM [5]. It is intriguing that oxidative stress and insulin resistance are intimately linked to each other, and it has been suggested that oxidative stress contributes to the pathogenesis of diabetes, hypertension, endothelial dysfunction and atherosclerosis under insulin resistance conditions [6]. Furthermore, fructose-fed rats demonstrate enhanced liver oxidative damage due to the increased burden of fructose metabolism [7].

Thus, there is a pressing need for the discovery of novel dietary functional ingredients for the treatment of insulin resistance and T2DM by combating glycemic control alterations. Among all such agents, polyphenolic compounds have attracted the interest of the scientific community and had been thoroughly investigated for this purpose in recent years [8]. Pterostilbene (PT) ($C_{16}H_{16}O_3$; Table 1), a polyphenolic stilbene derivative, has been reported to provide several health benefits in diabetes, dyslipidemia and cardiovascular diseases [9–11]. Although PT ameliorated glucose homeostasis in obesogenic (high fat) diet-induced insulin resistant rats by increasing GLUT4 expression, glucokinase activity and phosphorylated-Akt/total Akt ratio [12], its effects on other metabolic complications associated with insulin resistance have

Abbreviations: T2DM, Type 2 diabetes mellitus; PT, Pterostilbene; C, Control; D, Diabetic; M, Metformin; OGTT, Oral glucose tolerance test; FBG, Fasting blood glucose; FSI, Fasting serum insulin; ISI, Insulin sensitivity index; HOMA-IR, Homeostasis model of insulin resistance; ELISA, Enzyme-linked immunosorbent assay; HbA1c, Glycated hemoglobin; TC, Total cholesterol; TG, Triglycerides; HDL-C, High-density-lipoprotein-cholesterol; LDL-C, Low-density lipoprotein-cholesterol; VLDL-C, Very low-density lipoprotein-cholesterol; AAI, Antiatherogenic index; TBARS, Thiobarbituric acid reactive substances; SOD, Superoxide dismutase; GSH, Glutathione; SEM, Standard error mean; AUG, Area under the curve of blood glucose.

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not been well studied in this model. Moreover, the potential effects of PT on insulin resistance and its associated oxidative stress and metabolic complications induced by high fructose diet consumption have not been investigated in depth as yet.

In this context, the objective of the current investigation was to explore the efficacy of PT on insulin resistance, glycemic control, dyslipidemia and hepatic oxidative stress in high fructose (65%) diet-induced insulin resistant rats, a well-established T2DM model [13,14]. This study could help to better understand the antidiabetic mechanism of PT, especially in the context of the modulation of insulin resistance and oxidative stress.

2. Methods

2.1. Animals and experimental groups

The current protocol was executed in agreement with the principles of the Guide for the Care and Use of Laboratory Animals, published by the National Institutes of Health (NIH publication no. 86–23, revised 1996), and all animal experiments were undertaken with the approval of Institutional Animal Ethical Committee of Institute of Medical Sciences (Banaras Hindu University), Varanasi. Male Sprague-Dawley rats with initial body weight of 262 ± 15 g were procured from the Institute of Medical Science and were maintained at maintained at 25 °C under a 12-hour light/12-hour dark cycle. After two weeks of adaptation period, animals with a body weight of 330 ± 30 g were randomly segregated into five groups ($n = 10$).

Group-I	Control (C)	Rats received 65% corn starch (Research Diet, USA) and vehicle (10% β-cyclodextrin) for an interval of eight weeks.
Group-II	Diabetic (D)	Rats received 65% fructose diet (Research Diet, USA) for an interval of eight weeks for the induction of an established model of T2DM [14]. Vehicle (10% β-cyclodextrin) was given orally for eight weeks.
Group-III	D + PT20	Rats received 65% fructose diet along with pterostilbene (PT) 20 mg/kg/day for an interval of eight weeks. PT was dissolved in 10% β-cyclodextrin and given orally to rats.
Group-IV	D + PT40	Rats received 65% fructose diet along with PT 40 mg/kg/day for an interval of eight weeks. PT was dissolved in 10% β-cyclodextrin and given orally to rats.
Group-V	D + M	Rats received 65% fructose diet along with metformin (M) 100 mg/kg/day for an interval of eight weeks [15]. Metformin was dissolved in 0.9% saline and given orally to rats.

In experimental studies, PT was administered as a prophylactic modality for various diseases; Gomez-Zorita et al. found that PT administered as a dietary supplement for six weeks to obesogenic rats ameliorated insulin resistance and glycemic control through stimulation of Akt pathway [12]. Lv et al. reported that PT administration 5 min before reperfusion decreased cardiac infarct size by inhibiting neutrophil infiltration and the rise of serum TNF-α levels in normal rats [16]. Thus, we chose prophylactic administration of PT and metformin along with fructose induction for the amelioration of T2DM development.

2.2. Biochemical study

The body weights of all rats were measured each week during the experimental period. At the end of the eight-week study period, all animals were killed by cervical dislocation, and liver tissues were collected. Blood was collected via cardiac puncture and centrifuged at 4000 rpm for 15 min at 4 °C to isolate serum. Both serum and liver samples were stored in the freezer at −80 °C for further biochemical estimations.

2.3. Oral glucose tolerance test (OGTT)

One day before culling, all the rats from every group were fasted overnight to perform OGTT. A glucose load of 2 g/kg was administered orally to all of the experimental rats. Blood was collected from the tip of the tail at 0, 15, 30, 45, 60, 75, 90 and 120 min time intervals to quantify the blood glucose level using glucometer (One Touch Ultra).

2.4. Estimation of fasting blood glucose (FBG), fasting serum insulin (FSI) and insulin sensitivity index (ISI) and homeostasis model of insulin resistance (HOMA-IR)

The FBG levels were estimated on each week during the entire experimental period using the blood glucometer (One Touch Ultra). The FSI levels were evaluated by rat insulin enzyme-linked immunosorbent assay (ELISA) kit (Thermo Fisher Scientific, USA), performed according to the manufacturer's protocol. The ISI was derived from the following equation: $\text{ISI} = \text{Ln}\,(1/\text{FSI} \times \text{FBG})$. HOMA-IR is considered as the gold standard for the estimation of insulin resistance and can be derived using the equation [17]: $\text{HOMA-IR} = [\text{FBG (mmol/L)} \times \text{FSI (mU/L)}]/22.5$.

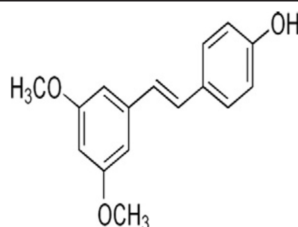
2.5. Determination of blood pressure

The experimental rats were transported to a quiet environment and placed in a chamber at an ambient temperature of 37 °C for 10 min, then placed in an acrylic restrainer. Systolic and diastolic blood pressures of rats were measured using the tail-cuff method (Narco Bio-System, Houston, TX) [18]. The mean of six successive recordings was calculated for each blood pressure measurement. Mean arterial pressure was calculated from the following formula: Mean arterial pressure = ⅔ diastolic blood pressure + ⅓ systolic blood pressure.

2.6. Estimation of glycated hemoglobin (HbA1c), hydrogen sulfide, peroxynitrite and uric acid

Serum HbA1c levels were estimated by the method described by Sudhakar and Pattabiraman [19]. Serum hydrogen sulfide levels were determined by the method of Cai et al. [20]. Serum peroxynitrite level as a marker of nitrosative-oxidative stress was measured according to the method described by Vanuffelen et al. [21]. Serum uric acid level was estimated by commercial diagnostic kits (Abcam, India), performed according to the manufacturer's protocol.

Table 1
Molecular structure of PT.



Molecular weight: 256.299 g/mol
Molecular formula: $C_{16}H_{16}O_3$
Other names: Dimethoxy resveratrol
3,5-Dimethoxy-4′-hydroxy-trans-stilbene
4-[2-(3,5-Dimethoxyphenyl)ethenyl]phenol

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