Abstract

Resveratrol is a polyphenolic phytoalexin produced in appreciable amounts as a secondary metabolite in grapevines in response to fungal infections. Based on the present knowledge, it appears to be a promising bioactive natural molecule with potential applications in phytotherapy or pharmacology. The present study was aimed to evaluate the antidiabetic properties of resveratrol in streptozotocin-nicotinamide induced experimental diabetes in rats. The diabetic rats orally treated with resveratrol (5 mg kg\(^{-1}\) b.w\(\times\) d\(^{1}\)) for 30 days resulted in significant (\(p < 0.05\)) decrease in the levels of blood glucose, glycosylated hemoglobin, blood urea, serum uric acid, serum creatinine and diminished activities of pathophysiological enzymes such as aspartate transaminase (AST), alanine transaminase (ALT) and alkaline phosphatase (ALP). The antihyperglycemic nature of resveratrol is also evidenced from the improvement in the levels of plasma insulin and hemoglobin. Further, the results are comparable with glyclazide, an oral standard drug. Thus, the present findings suggest that resveratrol may be considered as an effective therapeutic agent for the treatment of diabetes mellitus.

1. Introduction

Diabetes mellitus, characterized mainly by chronic hyperglycemia, is a progressively debilitating metabolic disorder of epidemic proportions and is estimated to afflict 5—7% of the population [1]. The pathophysiological mechanisms leading to diabetes can involve an inappropriate secretion of insulin or insulin resistance or both [2]. Hyperglycemia can lead to a reduced number of glucose transporters, down regulation in the number of insulin receptors as well as defects of tissue insulin signal transduction. Subsequent to these deteriorations, there is an absolute increase in hepatic glucose output, which exceeds an increase of glucose utilization, and fasting hyperglycemia occurs [3]. Finally, hyperglycemia itself manifests adverse effects on β-cell insulin secretion and on insulin resistance [4]. This process leads to long-term damage, dysfunction, and failure of various organs, especially the eyes, kidneys, nerves, heart, and blood vessels, and creates a huge economic burden related to the management of diabetic complications [5]. Given the alarming increase in the worldwide diabetic population, there is a need for novel therapies which are effective with minimal adverse events [6].

Several management strategies have been proposed for the early stages of hyperglycemia, with the aim of preventing the development of diabetes and associated complications. The current treatments of diabetes mellitus include diet, exercise, various oral antidiabetic drugs and insulin therapy [7]. The modern drugs, insulin and other oral hypoglycemic agents such as biguanides, sulphonylureas, α-glucosidase inhibitors have characteristic profile of adverse effects, which include frequent diarrhea, hypoglycemia, hepatotoxicity, lactic acidosis, dyslipidemia, hypertension, and hypercoagulability [8]. Significantly, for effective control of diabetes, combination therapy is being considered because no single
drug is able to target diabetes and its associated complications. This necessitates the identification of novel drugs which might function in a mechanistically distinct fashion to the existing drug targets [9]. Hence, the search for a definitive cure for diabetes mellitus is being pursued vigorously by the scientific community.

Plants have always been an exemplary source of drugs and many of the currently available drugs have been derived directly or indirectly from them. A wide array of plant derived active principles representing numerous chemical compounds has demonstrated activity consistent with their possible use in the treatment of diabetes mellitus [10]. In order to find a substance that has the therapeutic potential of oral hypoglycemic agent and exhibits additional pancreas-protecting effects, we have assessed the antihyperglycemic effects of resveratrol (3,4,5′-trihydroxystilbene), a phytoalexin found in grapes, mulberries, and peanuts, in streptozotocin-nicotinamide induced diabetic rats.

Phytoalexins are a group of phytochemicals of low molecular weight which are inhibitory to microorganisms and whose accumulation in plants is initiated by interaction of the plant with microorganisms [11]. Resveratrol formation in grape leaves has been correlated with disease resistance i.e. resveratrol is produced by the plant to defend itself against fungal and other attacks [12]. Resveratrol accounts for 5–10% of the biomass of grape skins, and its concentrations measured in a sampling of red wine varieties ranged from 2 to 40 μM [13]. Resveratrol was first isolated from the roots of white hellebore (Veratrum grandiflorum) in 1940, and later, in 1963, from the roots of Polygonum cuspidatum [14], a plant used in traditional Chinese and Japanese medicine for the treatment of human fungal, inflammatory, hypertensive, allergic and lipid diseases [15]. The protective properties of resveratrol observed in vitro and in vivo and its accumulation in red wine had led the scientific community to deem that this is the substance competent for the “French paradox”: the phenomenon that the frequent consumption of red wine in France is associated with a reduced mortality due to coronary heart disease and cancer as compared with other European countries [16].

Furthermore, resveratrol has been reported to elicit many cellular responses including cell cycle arrest, differentiation, and apoptosis [17], and has anti-inflammatory, anti-leukemic, antiviral, and neuroprotective properties [18–20]. Resveratrol can also function as an antioxidant [21] and reduces the risk of developing coronary heart disease, likely through its modulation of lipid metabolism and prevention of the low-density lipoprotein oxidation [22], as well as inhibition of eicosanoid production and platelet aggregation [23]. Resveratrol can inhibit several important enzymes involved in carcinogenesis, including ribonucleotide reductase [24], and human cytochrome P450 [25]. However, no systematic studies exist in the literature on the effect of resveratrol in experimental models of diabetes. Therefore, the present study was aimed to investigate the antidiabetic effect of resveratrol in streptozotocin-nicotinamide induced experimental diabetic rats.

2. Materials and methods

2.1. Chemicals

Resveratrol, streptozotocin and nicotinamide were procured from Sigma Chemicals Co. (St. Louis, MO, USA) and were stored at 2–4 °C and protected from light. All other chemicals used in this study were of the analytical grade.

2.2. Experimental animals

The animal experiments were designed and performed in accordance with the ethical norms approved by Ministry of Social Justices and Empowerment, Government of India and Institutional Animal Ethics Committee Guidelines (Approval No.01/036/07). Adult, male albino rats of Wistar strain weighing 160–180 g, procured from Tamilnadu Veterinary and Animal Sciences University, Chennai, Tamilnadu, were chosen as animal model for this study. They were maintained in clean, sterile, polypropylene cages and fed with commercial pellet rat chow (Hindustan Lever Ltd., Bangalore, India) and water ad libitum. After randomization into various groups, the rats were quarantined for a period of 2 weeks for environmental and trainer handling acclimatization before initiation of experiment. All animal manipulations were carried out in the morning to minimize the effects of circadian rhythm.

2.3. Induction of experimental diabetes

Experimental diabetes was induced by single intraperitoneal injection of streptozotocin (50 mg kg⁻¹) dissolved in 0.1 M of cold citrate buffer (pH 4.5) [26]; 15 min after the intraperitoneal administration of nicotinamide (110 mg kg⁻¹) [27] in 12 h fasted rats. Because STZ is capable of inducing fatal hypoglycemia as a result of massive pancreatic insulin release, the rats were provided with 10% glucose solution after 6 h of STZ administration for the next 24 h to prevent hypoglycemia. Neither death nor any other adverse effect was observed. After a week in time for the development and aggravation of diabetes, rats with moderate diabetes (i.e. blood glucose concentration, >250 mg dl⁻¹) that exhibited glycosuria and hyperglycemia were selected for the experiment.

2.4. Experimental design

After the successful induction of experimental diabetes, the rats were divided into five groups each comprising a minimum of six rats.

Group 1: Control rats.
Group 2: Control rats administered with resveratrol (5 mg kg⁻¹ b.w d⁻¹) in aqueous solution orally for 30 days.
Group 4: Diabetic rats administered with resveratrol (5 mg kg⁻¹ b.w d⁻¹) in aqueous solution orally for 30 days.
Group 5: Diabetic rats administered with glyclazide (5 mg kg\(^{-1}\) b.w d\(^{-1}\)) in aqueous solution orally for 30 days [28].

Body weight, blood glucose level measurements, food and water consumption calculations, and physical examinations were conducted periodically. The dosage was adjusted every week according to any change in body weight to maintain similar dose per kg body weight of rat over the entire period of study for each group. In addition, the skin, eyes, respiratory systems, autonomic and central nervous system conditions, and behavioral changes were examined daily. At the end of the experimental period, the rats were fasted overnight, anaesthetized and sacrificed by cervical decapitation. The blood was collected with or without EDTA for plasma or serum separation respectively.

2.5. Oral glucose tolerance test

At the end of the experimental period, fasting blood samples were taken from all the groups of rats. Four more blood samples were collected at 30, 60, 90 and 120 min intervals after administration of glucose solution at a dosage of 2 g kg\(^{-1}\) body weight. All the blood samples were collected with EDTA for the estimation of glucose by O-toluidine method [29].

2.6. Biochemical estimations

Fasting blood glucose was estimated by O-toluidine method [29]. Hemoglobin and glycosylated hemoglobin were estimated according to the methods of Drabkin and Austin [30] and Nayak and Pattabiraman [31], respectively. The plasma was separated and used for the assay of insulin using RIA assay kit (for rats) supplied by Linco Research, Inc. (USA) and the plasma protein was determined according to the method of Lowry et al. [32]. Blood urea [33], serum creatinine [34], and uric acid [35] were also assessed. The activities of pathophysiological enzymes such as serum aspartate transaminase (AST), serum alanine transaminase (ALT) and serum alkaline phosphatase (ALP) were assayed by the method of King [36,37].

2.7. Statistical analysis

The results were expressed as mean ± SEM of six rats per group and the statistical significance was evaluated by one-way analysis of variance (ANOVA) using the SPSS (version 15.0) program followed by LSD. Values were considered statistically significant when \(p < 0.05\).

3. Results

Fig. 1 exemplifies the effect of oral supplementation of resveratrol for 30 days on body weight changes in control and experimental groups of rats. During the experimental period, there was a significant \((p < 0.05)\) decrease in the body weight of diabetic rats compared with that of control rats. However, this significant weight loss is prevented in diabetic rats orally treated with resveratrol as well as glyclazide. This suggests that resveratrol as well as glyclazide treatment can prevent the body weight loss in diabetes. However, there is no significant \((p < 0.05)\) change in body weight in rats treated with resveratrol alone.

The effect of resveratrol as well as glyclazide supplementation on the blood glucose concentration in control and experimental groups of rats receiving an oral glucose challenge is shown in Fig. 2. The blood glucose concentration in the control rats was elevated to a maximum value at 60 min after glucose load and declined to near basal levels at 120 min, whereas, in STZ-nicotinamide induced diabetic rats, the peak increase in blood glucose level was noticed even after
60 min and remained high over the next 60 min. Supplementation with resveratrol as well as glyclazide to diabetic rats elicited significant ($p < 0.05$) decrease in blood glucose level at 60 min when compared with untreated diabetic rats. However, there is no significant ($p < 0.05$) alteration in the rats administered with resveratrol when compared with control rats.

Table 1 represents the effects of resveratrol on blood glucose, hemoglobin, glycosylated hemoglobin, plasma insulin and urine sugar of control and experimental groups of rats. The streptozotocin-nicotinamide induced diabetic rats showed a markedly higher blood glucose level than that of control rats, whereas the elevated blood glucose level was significantly ($p < 0.05$) reduced in diabetic rats orally supplemented with resveratrol as well as glyclazide. In addition, the elevated levels of glycosylated hemoglobin and decreased levels of hemoglobin and plasma insulin of diabetic groups of rats were significantly ($p < 0.05$) reverted to near normal levels by the administration of resveratrol as well as glyclazide to diabetic rats. However, no statistical ($p < 0.05$) different was noted in the rats treated with resveratrol alone compared to control rats. The urine sugar found in the diabetic rats was drastically controlled by the oral supplementation of resveratrol as well as glyclazide.

The effects of resveratrol on the levels of total protein, blood urea, serum creatinine and serum uric acid in control and experimental groups of rats are shown in Table 2. There were no significant ($p < 0.05$) changes in the levels of these parameters in control rats treated with resveratrol alone. However, these levels were significantly ($p < 0.05$) altered in diabetic group of rats when compared to control group of rats and were significantly ($p < 0.05$) reverted back to near normalcy by the oral administration of resveratrol as well as glyclazide.

Table 3 depicts the data on the effect of resveratrol in the activities of serum AST, ALT and ALP of control and experimental groups of rats. The activities of AST, ALT and ALP were increased significantly ($p < 0.05$) in serum of diabetic group of rats when compared to control group of rats. Oral treatment of resveratrol as well as glyclazide normalized the activities of these enzymes to near normalcy when compared to control group of rats.

4. Discussion

Streptozotocin is 1-methyl-l-nitrosourea attached to the carbon-2 position of glucose that causes β-cell necrosis and induces “experimental diabetes” in many animal models [38].
The glucose moiety of STZ allows preferential uptake of STZ into β-cells, probably via the glucose transporter-2 (GLUT-2), which are abundantly expressed in rodent β-cells of the pancreas. Because STZ is an alkylating agent, it causes DNA strand breaks that induce the activation of poly-ADP-ribose synthetase followed by lethal nicotinamide adenine dinucleotide (NAD) depletion [39]. In addition, intracellular metabolism of STZ aggravates the situation by yielding potential free radicals such as nitric oxide which also precipitates the additional DNA strand breaks [40].

It has been reported that administration of nicotinamide, a poly-ADP-ribose synthetase inhibitor, protected the islets’ functionality by protecting the decrease in the levels of NAD and proinsulin thereby partially reversing the inhibition of insulin secretion to prevent the aggravation of experimental diabetes following the administration of β-cell toxins, such as, streptozotocin and alloxan [41]. This condition contributes a number of features similar with T2DM, and is exemplified by stable hyperglycemia, glucose intolerance, and significantly altered glucose-stimulated insulin secretion both in vivo and in vitro [27]. Hence, in the present study, STZ-nicotinamide induced diabetes in experimental rats was chosen as the animal model to evaluate the antihyperglycemic potential of resveratrol.

The optimum dose of resveratrol was fixed by administering graded doses of resveratrol to diabetic rats for different time periods and the minimum effective dose for 30 days which caused maximum hypoglycemic activity and non-toxic nature was chosen (5 mg kg⁻¹ body weight) for the present study (data not shown). The destruction of β-cells during diabetes ultimately causes physico-metabolic abnormalities such as a decrease in body weight gain, and increase in food and water intake [42]. In addition, diabetic rats showed a clear muscle atrophy involving a decrease in both skeletal muscle mass and protein content. This was accompanied by a marked loss of total carcass nitrogen. These changes were related to important alterations in protein turnover in skeletal muscle [43]. Hence, a notable decrease in the body weight change observed in the diabetic group of rats might be the result of protein wasting due to the unavailability of carbohydrates for energy metabolism and the loss or degradation of structural proteins [44]. The improvement in body weight gain in diabetic rats supplemented with resveratrol highlight the blood glucose homeostasis which in turn promotes the body weight gain.

STZ-nicotinamide induced diabetes is mainly attributed to diabetic oxidative stress brought about by overproduction of free radicals which in turn exerts deleterious effect on the function of β-cells. Insulin deficiency ultimately results in increased production of glucose by the liver, and decreased utilization of glucose in peripheral tissues [45]. The elevated blood glucose level observed in the diabetic rats was significantly decreased in resveratrol treated group of rats suggesting insulin stimulatory effect of resveratrol from the remnant β-cells. This was further evidenced from the observed increase in the level of plasma insulin in diabetic rats treated with resveratrol.

Persistent hyperglycemia results in glycation of hemoglobin that leads to the formation of glycosylated hemoglobin [46]. Glycosylated hemoglobin is an easily measurable biochemical marker that strongly correlates with the level of ambient glycemia during a 2- to 3-month period and is a more accurate and reliable measure than fasting blood glucose level [47]. The concentration of glycosylated hemoglobin strongly predicts the risk of eye, kidney, and nerve disease in diabetes mellitus and is regarded as a key target for the diagnosis and prognosis of diabetes-related complications [48]. The observed increase in the level of glycosylated hemoglobin in the experimental diabetic rats implies the oxidation of sugars, extensive damage to both sugars and proteins in the circulation, vascular wall and lens proteins, continuing and reinforcing the cycle of oxidative stress and damage [49]. Oral treatment with resveratrol significantly decreased the levels of glycosylated hemoglobin, suggesting that it may prevent oxidative damage caused by the glycation reaction in diabetic conditions. These results on glucose and glycosylated

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### Table 2

<table>
<thead>
<tr>
<th>Groups</th>
<th>Total protein (g dl⁻¹)</th>
<th>Blood urea (mg dl⁻¹)</th>
<th>Serum creatinine (mg dl⁻¹⁻¹)</th>
<th>Serum uric acid (mg dl⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>9.19 ± 0.12</td>
<td>23.45 ± 0.65</td>
<td>0.43 ± 0.08</td>
<td>2.41 ± 0.07</td>
</tr>
<tr>
<td>Control + Resveratol</td>
<td>8.89 ± 0.11</td>
<td>23.03 ± 0.77</td>
<td>0.42 ± 0.01</td>
<td>2.62 ± 0.05</td>
</tr>
<tr>
<td>Diabetic control</td>
<td>6.22 ± 0.10*</td>
<td>44.86 ± 0.61**</td>
<td>1.06 ± 0.04b*</td>
<td>6.41 ± 0.13**</td>
</tr>
<tr>
<td>Diabetic + Resveratol</td>
<td>7.96 ± 0.12**</td>
<td>27.38 ± 0.55**</td>
<td>0.54 ± 0.02e*</td>
<td>2.98 ± 0.04*</td>
</tr>
<tr>
<td>Diabetic + Glyclazide</td>
<td>8.28 ± 0.10f*</td>
<td>24.93 ± 0.80f*</td>
<td>0.55 ± 0.01f*</td>
<td>2.91 ± 0.04f*</td>
</tr>
</tbody>
</table>

Values are given as mean ± SEM for groups of six rats in each. Values are statistically significant at *p < 0.05. Statistical significance was compared within the groups as follows: *Control + Resveratol treated rats were compared with control rats; **Diabetic rats were compared with control rats; *Diabetic + Resveratol and Diabetic + Glyclazide treated diabetic rats were compared with diabetic rats; †Diabetic + Resveratol treated rats were compared with Diabetic + Glyclazide rats.

### Table 3

<table>
<thead>
<tr>
<th>Groups</th>
<th>AST</th>
<th>ALT</th>
<th>ALP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>86.75 ± 0.69</td>
<td>20.32 ± 0.76</td>
<td>73.08 ± 1.01</td>
</tr>
<tr>
<td>Control + Resveratol</td>
<td>85.01 ± 0.56</td>
<td>20.61 ± 0.93</td>
<td>71.88 ± 0.62</td>
</tr>
<tr>
<td>Diabetic control</td>
<td>126.71 ± 1.31b*</td>
<td>47.17 ± 0.75b*</td>
<td>140.44 ± 0.99b*</td>
</tr>
<tr>
<td>Diabetic + Resveratol</td>
<td>94.57 ± 1.18cde*</td>
<td>24.91 ± 0.39c*</td>
<td>80.51 ± 0.54cde*</td>
</tr>
<tr>
<td>Diabetic + Glyclazide</td>
<td>91.65 ± 0.71c*</td>
<td>25.41 ± 0.72c*</td>
<td>78.08 ± 0.74c*</td>
</tr>
</tbody>
</table>

The enzyme activities are expressed as: AST and ALT – μmol of pyruvate h⁻¹ mg⁻¹ of protein; ALP – μmol of phenol liberated min⁻¹ mg⁻¹ of protein. Values are given as mean ± SEM for groups of six rats in each. Values are statistically significant at *p < 0.05. Statistical significance was compared within the groups as follows: *Control + Resveratol treated rats were compared with control rats; †Diabetic rats were compared with control rats; ‡Diabetic + Resveratol and Diabetic + Glyclazide treated diabetic rats were compared with diabetic rats; †Diabetic + Resveratol treated rats were compared with Diabetic + Glyclazide rats.
hemoglobin levels indicate the beneficial effects of resveratrol in preventing the pathogenesis of diabetic complications caused by impaired glucose metabolism.

An oral glucose tolerance test is a more sensitive measure of early abnormalities in glucose regulation than fasting plasma glucose or glycosylated hemoglobin [50]. Impaired glucose tolerance reflects hepatic gluconeogenesis and reduced uptake of glucose from blood into skeletal muscle and adipose tissue following a meal [51]. Impaired glucose tolerance serves as a marker for the state of insulin resistance and predicts both large and small-vessel vascular complications [52]. The impaired glucose tolerance observed in diabetic group of rats was corrected to near normal by the treatment with resveratrol further suggests the insulin stimulatory effects of resveratrol.

The absolute or relative deficiency of insulin may be responsible for the decreased levels of hemoglobin in diabetic rats [53]. The observed decrease in the level of hemoglobin in diabetic rats may be due to the formation of glycosylated hemoglobin and the restoration of hemoglobin level was observed in diabetic rats treated with resveratrol and glycolazide for 30 days.

Insulin deprivation in diabetic state causes a profound increase in protein catabolism, especially in skeletal muscle. Moreover, this total muscle protein catabolism is due to a net increase in protein breakdown rather than a decline in protein synthesis [54]. The alterations in protein metabolism could indeed be responsible for many of the chronic complications of diabetes, since they may involve both structural and functional proteins. Imbalances between synthesis and catabolism of protein can have dramatic consequences in the metabolism of many tissues such as gut, skeletal muscle and heart [55]. Indeed, as a consequence of the diabetic state, there is a profound cachexia associated with massive urinary nitrogen loss, increased forebrain amino acid output, increased aminonitrogenemia, and decreased total body potassium [42]. However, it must be recognized that the chemically induced diabetes causes complex metabolic and hormonal disturbances such as increase in both glucagon and glucocorticoids, and it is therefore simplistic to attribute all the observed differences in protein loss solely to the absence of insulin [55]. The anti-diabetic property of resveratrol may account for the observed increase in the levels of plasma proteins in diabetic rats treated with resveratrol.

Urea is the main end product of protein catabolism in the body. Accumulation of urea nitrogen in experimental diabetes may due to the enhanced breakdown of both liver and plasma proteins [56]. Alterations in nitrogen homeostasis may lead to increased hepatic elimination of urea nitrogen and increased peripheral release of nitrogenous substances. Thus, the observed negative nitrogen balance may partly because of changes occurring within the hepatocytes [57]. The oral administration of resveratrol to diabetic rats significantly decreased the altered levels of blood urea suggesting the prophylactic role of resveratrol in protein metabolism.

Uric acid, one of the major endogenous water-soluble antioxidants of the body, has been thought to be a metabolically inert end product of purine metabolism [58]. Elevated levels of serum uric acid are due to either an increase in uric acid production or a decrease in its excretion [59]. There is accumulating evidence that increased oxidative stress is closely related to diabetes and its vascular complications [60]. Thus, the elevated levels of circulating uric acid levels may be an indicator that the body is trying to protect itself from the deleterious effects of free radicals by increasing the products of endogenous antioxidants, such as uric acid. Interestingly, uric acid prevents oxidative modification of endothelial enzymes and preserves the ability of endothelium to mediate vascular dilatation in the face of oxidative stress [61]. In the present study, the increased levels of serum uric acid observed in diabetic rats were restored to near normalcy by the administration of resveratrol indicating the free radical scavenging activity of resveratrol.

Creatinine is a byproduct of the breakdown of creatine and phosphocreatine, which are considered as an energy storage compounds in muscle. The serum creatinine concentration in diabetic state may vary based on a number of factors including diet composition, muscle mass and gender. Serum creatinine values also depend on the ability of the kidney to excrete creatinine. An elevation in creatinine usually occurs simultaneously with an increase in blood urea nitrogen. Creatinine concentration is often used as a variable not only to assess impairment of kidney function but also as clinical end point to detect treatment related toxic effects of compounds on the kidney in experimental animals [62]. In the present study, the oral treatment with resveratrol for 30 days significantly reduced the serum creatinine level. Therefore, it may be concluded that the early renal changes occurred in the diabetic rats were significantly improved by the oral administration of resveratrol.

The liver, a major site of insulin clearance and production of inflammatory cytokines, plays an important role in maintaining normal glucose concentrations during fasting and postprandially [63]. Loss of insulin effect on the liver leads to glycogenolysis, an increase in hepatic glucose and free fatty acid production. The excess in free fatty acids found in the insulin-resistant state is known to be directly toxic to hepatocytes. Putative mechanisms include cell membrane disruption at high concentration, mitochondrial dysfunction, toxin formation, and activation and inhibition of key steps in the regulation of metabolism [64].

Aminotransferases, such as alanine aminotransferase and aspartate aminotransferase measure the concentration of intracellular hepatic enzymes that have leaked into the circulation and serve as a marker of hepatocyte injury. Alkaline phosphatases act as markers of biliary function and cholestasis. It is hypothesized that elevation in ALT, AST and ALP are considered as predictors of diabetes [65]. Further, the elevation in the levels of these gluconeogenic enzymes whose gene transcription is suppressed by insulin could indicate impairment in insulin signaling rather than purely hepatocyte injury [66]. Other potential explanations for elevated aminotransferase in insulin-resistant states include oxidative stress from reactive lipid peroxidation, peroxisomal β-oxidation, and recruited inflammatory cells. The insulin-resistant state is also characterized
by an increase in proinflammatory cytokines such as tumor necrosis factor-α (TNF-α), which may also contribute to hepato-cellular injury [67].

The increased activities of ALT, AST and ALP in the serum of diabetic rats may be primarily due to the leakage of these enzymes from liver cytosol into blood stream as a consequence of the hepatotoxic effect of STZ [68]. However, diabetic rats treated with resveratrol for 30 days diminished the activity of these enzymes to their basal levels, suggesting the tissue protective nature of resveratrol.

In conclusion, since resveratrol possesses significant hypoglycemic activity without any side effects, it may be advocated as a potent adjunct for the treatment of diabetes.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi: 10.1016/j.biopha.2008.06.037.

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