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The sesame lignan sesamin attenuates vascular dysfunction in streptozotocin diabetic rats: Involvement of nitric oxide and oxidative stress

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ABSTRACT

The effect of chronic administration of sesamin was studied on aortic reactivity of streptozotocin diabetic rats. Male diabetic rats received sesamin for 7 weeks after diabetes induction. Contractile responses to KCl and phenylephrine and relaxation response to acetylcholine were obtained from aortic rings. Maximum contractile response of endothelium-intact rings to phenylephrine was significantly lower in sesamin-treated diabetic rats relative to untreated diabetics and endothelium removal abolished this difference. Meanwhile, endothelium-dependent relaxation to acetylcholine was significantly higher in sesamin-treated diabetic rats as compared to diabetic ones and pretreatment of rings with nitric oxide synthase inhibitor N(G)-nitro-L-arginine methyl ester significantly attenuated the observed response. Two-month diabetes also resulted in an elevation of malondialdehyde and decreased superoxide dismutase activity and sesamin treatment significantly improved these changes. Therefore, chronic treatment of diabetic rats with sesamin could prevent some abnormal changes in vascular reactivity in diabetic rats through nitric oxide and via attenuation of oxidative stress and tissue integrity of endothelium is necessary for its beneficial effect.

1. Introduction

Cardiovascular disorders continue to constitute major causes of morbidity and mortality in diabetic patients in spite of significant achievements in their diagnosis and treatment (Coccheri, 2007). Changes in vascular responsiveness to vasoconstrictors and vasodilators are mainly responsible for development of some vascular complications of diabetics (Nasri et al., 2011). Most of these complications are due to increased serum glucose and augmented generation of reactive oxygen species which finally lead to endothelium dysfunction (Naito et al., 2011).

Sesamin, one of the major lignans in sesame seed and oil, and its isomers have beneficial physiological effects, acting as an antioxidant (Ikeda et al., 2003), anti-carcinogen (Hirose et al., 1992), anti-hypertensive (Kita et al., 1995; Nakano et al., 2003) and are capable of reducing serum lipids (Rogi et al., 2011). There are also indications that sesamin isomers could enhance plasma levels of α- and γ-tocopherol in rats (Yamashita et al., 1995). Recent work demonstrated that sesamin metabolites induce nitric oxide-dependent vasorelaxation in vitro (Nakano et al., 2006) and sesamin feeding enhances endothelium-dependent relaxation in deoxycorticosterone acetate-salt hypertensive rats (Nakano et al., 2003). It has also been reported that the aqueous leaf extract of sesame induces dose-dependent vasorelaxation in guinea-pig aortas (Konan et al., 2008). Nevertheless, the exact underlying mechanisms of in vivo protective effects of sesamin on vascular system are not completely understood. Therefore, this study was undertaken to assess the beneficial effect of chronic sesamin treatment on aortic reactivity of streptozotocin-diabetic rats and to investigate the involvement of nitric oxide, prostanoids, and oxidative stress.

2. Materials and methods

2.1. Animals

Male albino Wistar rats ($n=48$) (Pasteur's institute, Tehran, Iran) weighing 240–300 g were housed in an air-conditioned colony room at 21 ± 2 °C and supplied with standard pellet diet and tap water ad libitum. Procedures involving animals and their care were

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conducted in conformity with NIH guidelines for the care and use of laboratory animals.

2.2. Experimental protocol

The rats were rendered diabetic by a single intraperitoneal dose of streptozotocin (60 mg/kg) freshly dissolved in ice-cold 0.1 M citrate buffer (pH 4.5). Age-matched normal animals that received an injection of an equivalent volume of buffer comprised a non-diabetic control group. One week after streptozotocin injection, overnight fasting blood samples were collected and serum glucose concentrations were measured using glucose oxidation method (Zistchimie, Tehran). Only those animals with a serum glucose level higher than 250 mg/dl were selected as diabetic. During the next weeks, diabetes was reconfirmed by the presence of polyphagia, polydipsia, polyuria, and weight loss. Normal and hyperglycemic rats were randomly allocated and similarly grouped into six groups (eight in each): normal vehicle-treated control, sesamin-treated controls in two subgroups, diabetic, and sesamin-treated diabetics in two subgroups. Sesamin was daily administered p.o. (using gavage needle) at doses of 10 and 20 mg/kg dissolved in 0.5% carboxymethylcellulose throughout the experimental period for 7 weeks. Changes in body weight were regularly recorded during the study.

Finally, the rats were anesthetized with diethyl ether, decapitated, descending thoracic aorta was carefully removed and placed in a petri dish filled with cold Krebs solution containing (in mM): NaCl 118.5, KCl 4.7, $CaCl_2$ 1.5, $MgSO_4$ 1.2, KH_2PO_4 1.2, $NaHCO_3$ 25, and glucose 11. The aorta was cleaned of excess connective tissue and fat and cut into rings of approximately 4 mm in length. Aortic rings were suspended between the bases of two triangular-shaped wires. One wire was attached to a fixed tissue support in a 50 ml isolated tissue bath containing Krebs solution (pH 7.4) maintained at 37 °C and continuously aerated with a mixture of 5% CO_2 and 95% O_2. The other end of each wire attached by a cotton thread to a F60 isometric force transducer (Narco Biosystems, USA) connected to a computer. In all experiments, special care was taken to avoid damaging the luminal surface of endothelium. Aortic rings were equilibrated at a resting tension of 1.5 g for at least 45 min. In some experiments, the endothelium was mechanically removed by gently rubbing the internal surface with a filter paper. Isometric contractions were induced by the addition of phenylephrine (1 μM) and once the contraction stabilized, a single concentration of acetylcholine (1 μM) was added to the bath in order to assess the endothelial integrity of the preparations. Endothelium was considered to be intact when this drug elicited a vasorelaxation $\geq$50% of the maximal contraction obtained in vascular rings precontracted with phenylephrine. The absence of acetylcholine relaxant action in the vessels indicated the total removal of endothelial cells. After assessing the integrity of the endothelium, vascular tissues were allowed to recuperate for at least 30 min.

At the end of the equilibration period, dose–response curves with KCl (10–50 mM) and phenylephrine (10^{-10}–10^{-5} M) in the presence and absence of endothelium were obtained in aortic rings in a cumulative manner. To evaluate acetylcholine (10^{-9}–10^{-4} M)-induced vasodilatation in rings with endothelium, they were preconstricted with a submaximal concentration of phenylephrine (10^{-6} M) which produced 70–80% of maximal response. The sensitivity to the agonists was evaluated as pD2, which is the negative logarithm of the agonist concentration required to produce 50% of the maximum response.

To determine the participation of nitric oxide, rings were incubated 30 min before the experiment with N(G)-nitro-L-arginine methyl ester (100 μM, a non-selective nitric oxide synthase inhibitor). To determine the participation of endothelial cyclooxygenase-derived prostanoids in response to acetylcholine, segments were preincubated with indomethacin (10 μM, an inhibitor of cyclooxygenase-derived prostanoid synthesis) 30 min before the experiment with acetylcholine.

After each vasoreactivity experiment, aortic rings were blotted, weighed, and the cross-sectional area (csa) was calculated using the following formula: Cross-sectional area (mm^2)=weight (mg)/[length (mm) × density (mg/mm^3)]. The density of the preparations was assumed to be 1.05 mg/mm^2 (Abebe et al., 1990).

2.3. Determination of malondialdehyde concentration in aortic rings

After removing aortic segments and cleansing them of extra tissues, they were blotted dry and weighed, then made into 5% tissue homogenate in ice-cold 0.9% saline solution. A supernatant was obtained from tissue homogenate by centrifugation (1000 × *g*, 4 °C, 5 min). The malondialdehyde concentration (thiobarbituric acid reactive substances) in the supernatant was measured as described before (Roghani and Baluchnejadmojarad, 2009). Briefly, trichloroacetic acid and thiobarbituric acid reactive substances reagent were added to supernatant, then mixed and incubated at 100 °C for 80 min. After cooling on ice, samples were centrifuged at 1000 × *g* for 20 min and the absorbance of the supernatant was read at 532 nm. Thiobarbituric acid reactive substances results were expressed as malondialdehyde equivalents using tetraethoxypropane as standard.

2.4. Measurement of superoxide dismutase activity in aortic rings

The superoxide dismutase activity of supernatant was measured as described earlier (Baluchnejadmojarad and Roghani, 2008). Briefly, supernatant was incubated with xanthine and xanthine oxidase in potassium phosphate buffer (pH 7.8, 37 °C) for 40 min and nitro blue tetrazolium was added. Blue formazan was then monitored spectrophotometrically at 550 nm. The amount of protein that inhibited nitro blue tetrazolium reduction to 50% maximum was defined as 1 nitrite unit of superoxide dismutase activity.

2.5. Drugs

Phenylephrine, sesamin, streptozotocin, acetylcholine, indomethacin, and N(G)-nitro-L-arginine methyl ester were purchased from Sigma Chemical (St. Louis, USA). All other chemicals were purchased from Merck (Germany) and Temad (Iran). Indomethacin solution was prepared in ethanol in such a way that the maximal ethanol concentration of the medium was less than 0.001% (v/v).

2.6. Data and statistical analysis

All values were given as means ± S.E.M. Contractile response to phenylephrine was expressed as grams of tension per cross-sectional area of tissue. Relaxation response for acetylcholine was expressed as a percentage decrease of the maximum contractile response induced by phenylephrine. Statistical analysis was carried out using repeated measure ANOVA (for body weight and serum glucose level) and one-way ANOVA (for data of vascular reactivity) followed by Tukey post-hoc test. A statistical *P* value less than 0.05 considered significant.

3. Results

After 8 weeks, the weight of the vehicle-treated diabetic rats was found to be significantly decreased as compared to controls

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($P<0.005$) and sesamin treatment did not improve it. Untreated diabetic rats had also an elevated serum glucose level over those of control rats ($P<0.0005$) and sesamin treatment of diabetic rats did not ameliorate hyperglycemia in diabetic rats (Fig. 1).

Cumulative addition of KCl (10–50 mM) and phenylephrine (10^{-10}–10^{-5} M) resulted in concentration dependent contractions in aortas of all groups (Figs. 2 and 3). The maximum contractile responses to KCl and phenylephrine in the aortas from vehicle-treated diabetic rats in the presence of endothelium were found to be significantly ($P<0.01$–0.005) greater than vehicle-treated control rats and concentration-response curve of endothelium-intact aortas from sesamin-treated diabetic rats (at a dose of 20 mg/kg) to phenylephrine was significantly attenuated compared to vehicle-treated diabetics (Table 1). Although endothelium-denuded aortic rings in all groups showed a higher contractile response to KCl and phenylephrine, the observed changes between treated and untreated diabetics were attenuated after endothelium removal. This clearly indicates the necessity of endothelium presence for beneficial vascular effect of sesamin. There were also no significant differences among the groups in terms of the pD2 (Table 1), indicating that there has not been any significant change in the sensitivity of aortic rings from different groups.

Addition of acetylcholine resulted in concentration-dependent relaxations in all aortic rings precontracted with phenylephrine (Fig. 4). As was expected, endothelium-dependent relaxation responses induced by acetylcholine was significantly lower in vehicle-treated diabetic rats compared to vehicle-treated controls ($P<0.05$–0.005). The existing difference between sesamin-treated (at a dose of 20 mg/kg) and vehicle-treated diabetic rats was only significant ($P<0.05$) at concentrations higher than 10^{-5} M.

Regarding relaxation response to acetylcholine, pre-incubation of aortic rings with N(G)-nitro-L-arginine methyl ester almost completely abolished the vasodilator response to acetylcholine in segments from sesamin20-treated diabetic rats, indicating the important role of endothelium-derived nitric oxide in the vascular effect of sesamin (Fig. 5). Pre-incubation of aortic segments from sesamin20-treated diabetic rats with indomethacin partly and non-significantly diminished the endothelial vasodilator response to acetylcholine (Fig. 6).

Regarding aortic oxidative stress markers (Table 2), streptozotocin-induced diabetes resulted in an elevation of malondialdehyde content and decreased superoxide dismutase activity in aortic tissue and chronic treatment of diabetic group with sesamin at a dose of 20 mg/kg significantly reversed the increased malondialdehyde content and reduced activity of superoxide dismutase.

4. Discussion

In this study, administration of sesamin for 7 weeks reduced the enhanced contractility of aortic rings to phenylephrine and increased acetylcholine-induced relaxation which was partly due

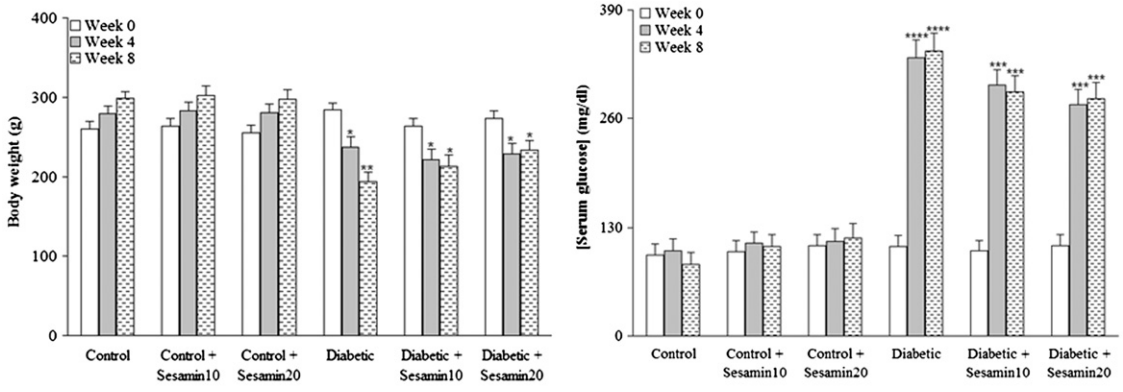

Fig. 1. Body weight (left panel) and serum glucose concentration (right panel) before and 4 or 8 weeks after induction of diabetes ($n=7$–8 for each group). $^{*}P<0.05$, $^{**}P<0.005$, $^{***}P<0.001$, $^{****}P<0.0005$ (as compared to week 0 in the same group).

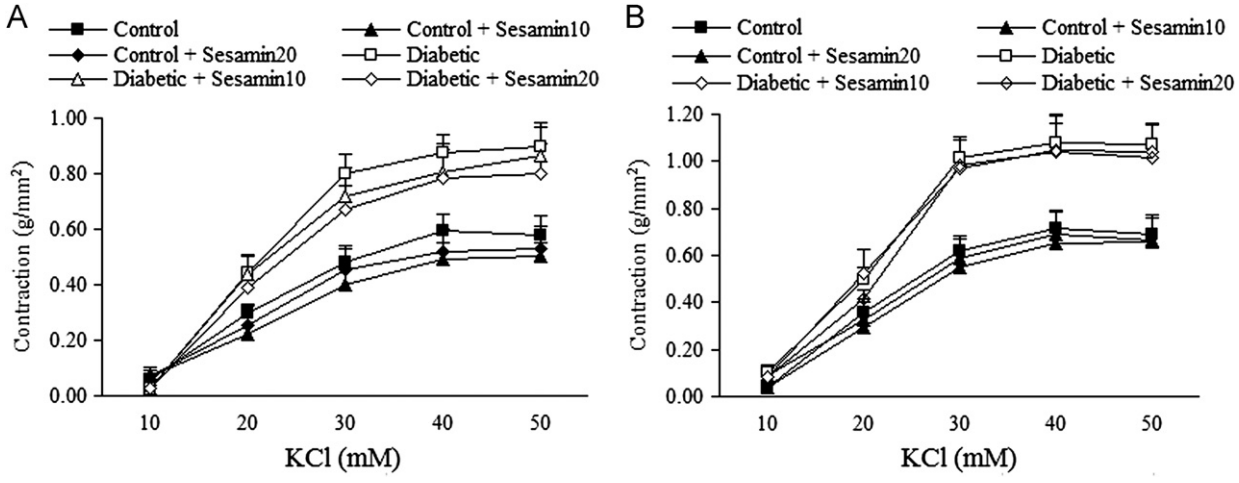

Fig. 2. Cumulative concentration-response curves for KCl in aortic preparations 8 weeks after induction of diabetes in the presence (*A*) and absence (*B*) of endothelium ($n=6$–8 for each group).

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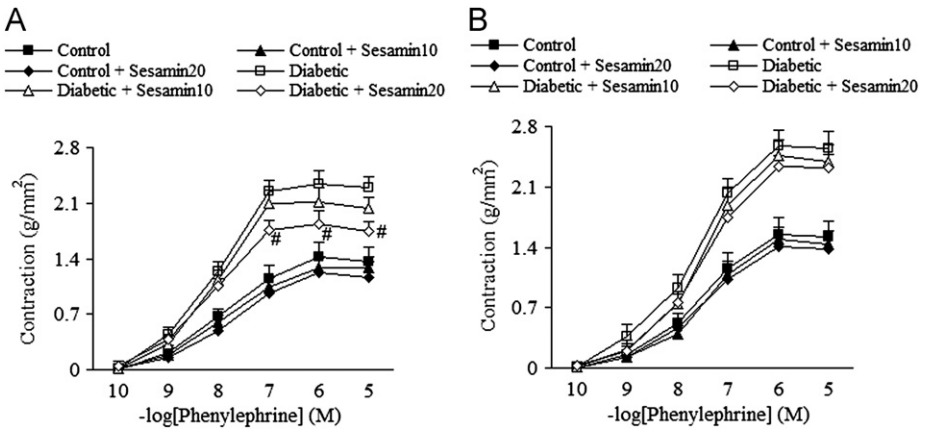

Fig. 3. Cumulative concentration–response curves for phenylephrine in aortic preparations 8 weeks after induction of diabetes in the presence (*A*) and absence (*B*) of endothelium ($n=6$–8 for each group). #$P<0.05$ (as compared to diabetic).

Table 1
Maximum responses and pD_2 values for agonists in aortic rings.

	pD_2		Maximum responses	
Endothelium intact	Phenylephrine	Acetylcholine	Phenylephrine	Acetylcholine
Control ($n=7$)	7.64 ± 0.23	7.28 ± 0.16	1.36 ± 0.18	73.4 ± 4.6
Control+Sesamin10 ($n=6$)	7.83 ± 0.21	7.15 ± 0.19	1.28 ± 0.14	78.8 ± 3.9
Control+Sesamin20 ($n=6$)	7.72 ± 0.19	7.18 ± 0.16	1.16 ± 0.19	83.5 ± 4.7
Diabetic ($n=7$)	7.91 ± 0.18	7.71 ± 0.22	2.29 ± 0.14[b]	36.2 ± 4.8[b]
Diabetic+Sesamin10 ($n=8$)	8.05 ± 0.21	7.54 ± 0.20	2.03 ± 0.14[a]	39.8 ± 4.5[b]
Diabetic+Sesamin20 ($n=8$)	8.15 ± 0.20	7.34 ± 0.18	1.67 ± 0.13[c]	55.2 ± 4.3[c]
Endothelium denuded				
Control ($n=6$)	7.46 ± 0.17	–	1.44 ± 0.16	–
Control+Sesamin10 ($n=6$)	7.54 ± 21	–	1.38 ± 0.21	–
Control+Sesamin20 ($n=7$)	7.53 ± 0.18	–	1.35 ± 0.17	–
Diabetic ($n=6$)	7.65 ± 0.22	–	2.39 ± 0.24	–
Diabetic+Sesamin10 ($n=6$)	7.68 ± 0.19	–	2.32 ± 0.18	–
Diabetic+Sesamin20 ($n=7$)	7.77 ± 0.16	–	2.27 ± 0.17	–

Data are expressed as means ± SEM. For phenylephrine and acetylcholine, maximum responses (E_{max}) are presented as g/mm^2 and percentage decrease of the maximum contractile response induced by PE, respectively.

[a] $P<0.05$.
[b] $P<0.005$ (versus control).
[c] $P<0.05$ (versus diabetic).

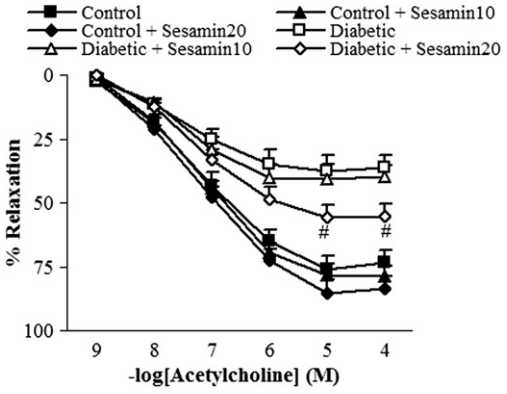

Fig. 4. Cumulative concentration–response curves for acetylcholine in endothelium-intact aortic rings precontracted with phenylephrine 8 weeks after induction of diabetes. Relaxation responses are expressed as a percentage of the submaximal contraction induced by phenylephrine which produced 70–80% of maximal response ($n=6$–8 for each group). #$P<0.05$ (as compared to diabetic).

to interference with the nitric oxide pathway, but not with cyclooxygenase-dependent prostanoids. In addition, endothelium removal clearly affected phenylephrine-induced contractions in sesamin-treated diabetic rats. Sesamin treatment also attenuated the increased malondialdehyde content and restored the activity of superoxide dismutase.

Vascular complications are the hallmarks of diabetes with hyperglycemia as one of the main causes (Madonna and De Caterina, 2011). Compared to the aortic rings from control animals, contraction of aortas to KCl and phenylephrine from diabetic rats was significantly stronger. This is consistent with previous studies (Roghani and Baluchnejadmojarad, 2009). Chronic sesamin was capable to attenuate this change only for phenylephrine-induced contractions. Impaired endothelial function (Olukman et al., 2010), enhanced sensitivity of calcium channels (Chang et al., 1993), an increase in vasoconstrictor prostanoids due to increased superoxide anions and increased sensitivity to adrenergic agonists (Abebe, 2008) might all be responsible for increased contractile responses in diabetic rats, which improves after sesamin treatment. Since KCl-induced contraction is through membrane depolarization rather than acting at a receptor level, therefore, changes in contractile responsiveness to KCl occur at the post-receptor level (Connolly et al., 1999) with the influx of Ca^{2+} through voltage-dependent Ca^{2+} channels in rat aorta (Bhugra and Gulati, 1996). In contrast, there are multiple and cascading pathways for induction of tonic contraction subsequent to α1-adrenoceptor activation due to phenylephrine that lead to Ca^{2+} influx through voltage-dependent

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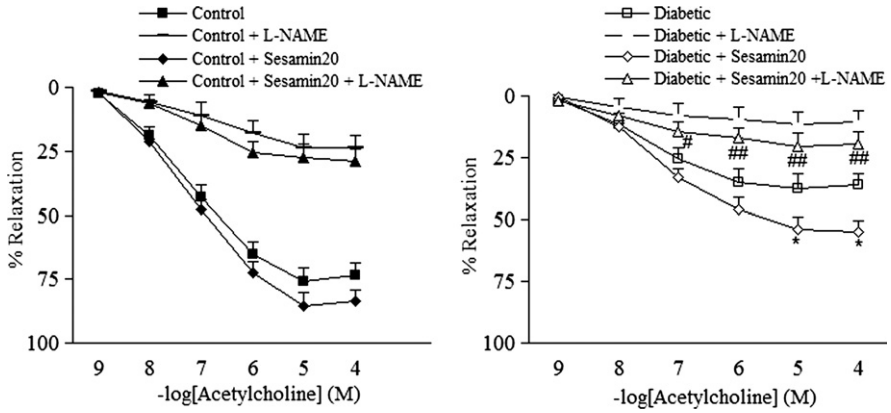

Fig. 5. Cumulative concentration-response curves for ACh in endothelium-intact aortic rings precontracted with phenylephrine in the presence and absence of L-NAME 8 weeks after induction of diabetes. Relaxation responses are expressed as a percentage of the submaximal contraction induced by phenylephrine which produced 70–80% of maximal response ($n=6$–7 for each group). L-NAME stands for N(omega)-L-arginine methyl ester. $^{*}p<0.05$ (as compared to diabetic) $\#p<0.01$, $\#\#p<0.005$ (as compared to diabetic+sesamin20).

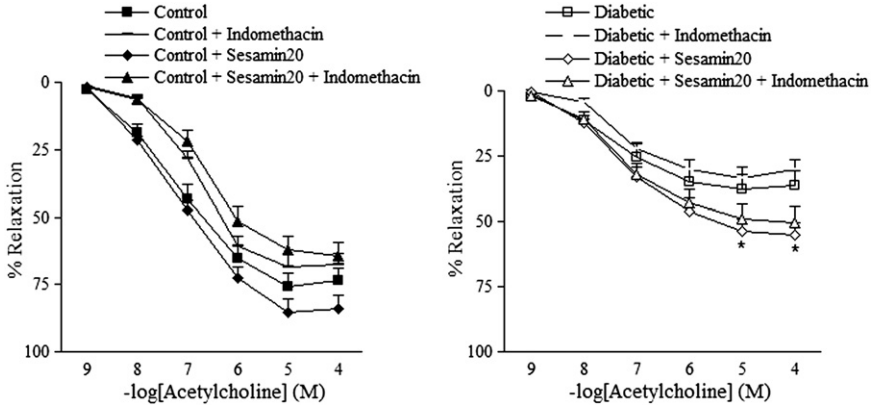

Fig. 6. Cumulative relaxation response to acetylcholine in aortic rings precontracted with phenylephrine in the presence and absence of indomethacin eight weeks after induction of diabetes. Relaxation responses are expressed as a percentage ($n=6$–7 for each group). $\#P<0.05$ (as compared to diabetic).

Table 2
Malondialdehyde content and superoxide dismutase activity in aortic tissue.

Groups	Malondialdehyde (μmol/g protein)	Superoxide dismutase activity (k nitrite unit/g protein)
Control ($n=7$)	5.7 ± 0.5	117 ± 6
Control+Sesamin10 ($n=6$)	5.8 ± 0.6	115 ± 7
Control+Sesamin20 ($n=6$)	5.5 ± 0.4	119 ± 7
Diabetic ($n=6$)	9.2 ± 0.7^{c}	76 ± 8^{b}
Diabetic+Sesamin10 ($n=5$)	8.3 ± 0.8^{a}	81 ± 9^{a}
Diabetic+Sesamin20 ($n=6$)	6.9 ± 0.5^{d}	105 ± 8^{d}

[a] $p<0.05$.
[b] $p<0.005$.
[c] $p<0.001$ (versus control).
[d] $p<0.05$ (versus diabetic).

Ca^{2+} channels (Nishimura et al., 1991). In the present study, sesamin significantly inhibited phenylephrine- but not KCl-induced contractions, confirming that beneficial effect of the sesamin may have been through several targets of action including possible changes in the sensitivity of α1 adrenoceptors and/or inhibition of the calcium release from the intracellular stores and reducing the sensitivity of contractile machinery to calcium and so forth, which itself needs further investigation. In other words, it is less likely that sesamin had been able to directly modify the functioning of the smooth muscle membrane calcium channels in this study.

In endothelial cells of most vascular beds, acetylcholine could stimulate production and release of endothelial-derived relaxing factors including nitric oxide, prostacyclin and endothelium-derived hyperpolarizing factor and in this way leads to relaxation of vascular smooth muscle in an endothelium-dependent manner (Flammer and Luscher, 2010; Takaki et al., 2008; Zhang et al., 2011). The acetylcholine-induced relaxation response is endothelium-dependent and nitric oxide-mediated (Roghani and Baluchnejadmojarad, 2009). The results of this work revealed that the endothelium-dependent relaxant response was reduced in aortas from streptozotocin-induced diabetic rats and this reduced relaxation was partially recovered by sesamin treatment. Although some researchers ascertained that the sensitivity to acetylcholine decreases in diabetes (Abebe, 2008), the results of this research, in accordance with those of many previous ones (Silan, 2008) reveals that diabetes condition in long-term only decrease the maximum responses to acetylcholine but not the sensitivity (pD2). Impaired endothelium-dependent relaxation in streptozotocin-induced diabetic rat might be due to increased blood glucose level and decreased blood insulin level. It has been shown that hyperglycaemia causes tissue damage with several mechanisms, including advanced glycation end product formation, increased polyol pathway flux, apoptosis and reactive oxygen species formation (Hartge et al., 2007). Our results showed that sesamin treatment could not exert a significant effect on glycemia in streptozotocin-induced diabetic rats; therefore, its beneficial effect on aortic tissue of diabetic rats should be due to mechanisms other than a hypoglycemic effect.

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Some damaging effect of diabetes on vascular tissue of diabetic animals is believed to be due to enhanced oxidative stress, as shown by enhanced malondialdehyde and decreased activity of defensive enzymes like superoxide dismutase (Baluchnejadmojarad and Roghani, 2008), as was observed in this study. This could also lead to diabetes-induced functional changes in vascular endothelial cells and the development of altered endothelium-dependent vasoreactivity. The results of the present study showed that chronic treatment of sesamin significantly decreased malondialdehyde content and enhanced superoxide dismutase activity in aortic tissue from diabetic rats, indicating that the improvement in vascular responsiveness from sesamin may be partly due to ameliorating lipid peroxidation and oxidative injury.

In conclusion, in vivo chronic treatment of diabetic rats with sesamin could dose-dependently prevent the functional changes in vascular reactivity through nitric oxide- and not prostaglandin-dependent pathways and via attenuation of aortic lipid peroxidation. Our data may be helpful in the development of new natural drugs to improve endothelial function and to prevent cardiovascular diseases.

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