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Antidiabetic Effect of *Salvia verticillata* L. Aerial Parts in Normal and Streptozotocin-induced Diabetic Rats

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Abstract: Herbal medicine has been used for many years by different cultures around the world for the treatment of diabetes. *Salvia verticillata* L. was investigated for its possible antidiabetic effect in normal and streptozotocin-induced diabetic rats. The animals were made diabetic using streptozotocin (70 mg kg⁻¹, i.p.). The ethanolic extract (0.05, 0.1 and 0.2 g kg⁻¹) were administered orally. The control groups were administered saline. Oral administration of ethanolic extract of *Salvia verticillata* aerial parts for 14 days on the level of serum glucose, total cholesterol, triacylglycerol, urea, uric acid, creatinine, aspartate aminotransferase and alanine aminotransferase in normal and streptozotocin-induced diabetic rats were evaluated. At the end of the experiment, rats were fasted overnight and blood samples were collected. A comparison was made between the action of extract and a standard antidiabetic drug, glibenclamide. Oral administration of 0.05, 0.1 and 0.2 g kg⁻¹ b.wt. of the ethanolic extract of *Salvia verticillata* aerial parts for 14 days exhibited a significant reduction in serum glucose, total cholesterol, triglycerides, urea, uric acid, creatinine, aspartate aminotransferase, alanine aminotransferase and increased plasma insulin in diabetic rats. It also prevents body weight loss in diabetic rats. The administration of extract did not change these serum parameters in normal rats. The antidiabetic effect of the extract was similar to that observed with glibenclamide. So, our study revealed the anti-diabetic potential of *Salvia verticillata* and this study could be helpful to develop medicinal preparations for diabetes and related symptoms.

Key words: *Salvia verticillata* L., hypoglycemic, hypolipidemic, streptozotocin

INTRODUCTION

Diabetes mellitus is a global disease that is a major cause of morbidity in the world. The worldwide prevalence of diabetes mellitus is expected to be more than 240 million by the year 2010 (McCarty and Zimmet, 1997). This disorder is basically characterized by high levels of blood glucose caused by defective insulin production and action that are often responsible for severe health problems and early death (Leahy, 2005). Diabetes is a major cause of disability and hospitalization. It can result in a range of complications that occur primarily in the arteries and capillaries. Diabetes patients, particularly those with type II diabetes are at considerable risk of excessive morbidity and mortality from cardiovascular, cerebrovascular and peripheral vascular diseases leading to myocardial infarction, strokes and amputations (Watkins, 2003).

Recent decades have shown a resurgent interest in traditional plant treatments for diabetes, which has pervaded nutrition, the pharmaceutical industry and academic research, fueled by a growing public interest and awareness of so-called complementary and natural types of medicine (Day, 1998). Many traditional plant treatments for diabetes exist, wherein lies a hidden wealth of potentially useful natural products for diabetes control (Gray *et al.*, 2000). Nonetheless, few traditional anti-diabetic plants have received scientific or medical scrutiny, despite recommendations by the WHO (1980) that this should be undertaken (Li *et al.*, 2004).

Salvia is an important genus consisting of about 900 species in the family Lamiaceae. Many species of *Salvia* are used as herbal tea and for food flavoring, as well as in cosmetics, perfumery and the pharmaceutical industries (Chalchat *et al.*, 1998). Consequently, extracts of different *Salvia* species have been examined for a

number of biological activities and their antimicrobial, anti-inflammatory, antioxidant, spasmolytic and cholinergic binding properties and involved mechanisms have been partially described (Cuvelier *et al.*, 1994; Baricevic and Bartol, 2001; Zupko *et al.*, 2001; Capasso *et al.*, 2004; Ren *et al.*, 2004). However, there are no scientific studies available on the antidiabetic effects of *Salvia verticillata* extract although this plant is used as a folk remedy for the treatment of diabetes. Therefore, the anti-diabetic effects of aerial parts of *Salvia verticillata* ethanolic extract was investigated in normal and streptozotocin (STZ)-induced diabetic rats.

MATERIALS AND METHODS

Subjects: Healthy male Wistar rats (weighing 200-250 g) were purchased from Institute Pasteur, Iran. The animals were kept in the animal house unit of the Department of Biology at the Islamic Azad University for 2 weeks to be acclimatized. The animals were housed in standard conditions of temperature ($21 \pm 2^\circ\text{C}$), humidity (40-60%) and a 12 h light-dark cycle. The rats were fed with commercial diet (35% carbohydrates, 25% proteins, 7% lipids and 3% vitamins) and tap water *ad libitum*. This research project was conducted from 1/2/2008 to 1/11/2009. Experimental procedures involving the animals and their care were conducted in conformity with the institutional guidelines that are in compliance with national and international laws and Guidelines for Care and Use of Laboratory Animals in Biomedical Research as adopted and promulgated by the World Health Organization and United States National Institutes of Health.

Chemicals: STZ was purchased from Pharmacia and Upjohn Company, USA. Glibenclamide was purchased from Sigma (St. Louis, MO, USA). All enzymes and biochemical reagents were purchased from Parsazmoon Company of Iran. All other chemicals used were of good quality and analytical grade.

Extraction of ethanolic plant material: Aerial parts of *Salvia verticillata* were collected from North of Iran in summer and identified in the I.A.U. Herbarium (Voucher number: 05558, deposited in: Islamic Azad University Herbarium). The aerial parts were shade dried and were finely powdered. The powder was extracted with 300 mL aqueous 80% ethanol using soxhelt apparatus (Hashemi Company, Iran) for 72 h. After extraction, the solvent was filtered and then evaporated by Rotavapor (Heidolph Company, Germany). The extract yield was 14%. The obtained *Salvia verticillata* alcoholic extract was stored at -20°C until usage.

Induction of experimental diabetes mellitus: Diabetes was induced in rats five days before starting the experiment. Diabetes was induced by a single injection of STZ (70 mg kg^{-1} b.wt.) freshly dissolved in sodium chloride (pH 3.5-4.5) into the intraperitoneum. Diabetes was confirmed by the determination of fasting blood glucose concentration with the help of a glucometer (ACON Company, USA) on the fifth day after administration of STZ. Rats with fasting serum glucose levels above 300 mg dL^{-1} were considered diabetic and were used in the subsequent experimental procedures (El-Fiky *et al.*, 1996). The blood concentration of glucose in normal rats was in the range of $80\text{-}110 \text{ mg dL}^{-1}$.

Experimental design: The randomized trial experiment was carried on nine groups (I-IX) of eight rats each:

- **Group 1:** Normal control
- **Groups 2-4:** Normal rats treated with 0.05, 0.1 and 0.2 g kg^{-1} b.wt. of extract, respectively
- **Group 4:** Diabetic control
- **Group 6-8:** Diabetic treated with 0.05, 0.1 and 0.2 g kg^{-1} b.wt. of extract, respectively
- **Group 9:** Diabetic rats treated with $600 \mu\text{g kg}^{-1}$ b.wt. of glibenclamide

Control rats (groups 1 and 5) received orally vehicle (distilled water) only while others groups received the extract or glibenclamide orally, suspended in distilled water. The drug preparations were fed orally by gastric intubation to rats of respective groups once daily for 14 days. The volume of administration was 1 mL and the treatments lasted for 14 days. Body weights of mice were recorded initially and at the end of the experiment.

Biochemical analysis: At the end of the experiment (14 days), rats were fasted overnight and blood samples were withdrawn through the retro-orbital plexus under light ether anesthesia using a glass capillary and collected in tubes. Blood was allowed to clot and serum separated by centrifugation (Kokusan, Japan) at 3500 rpm for 10 min. Blood glucose levels were determined by the glucose oxidase method using glucose diagnostic kits (Barham and Trinder, 1972). Plasma insulin was determined by using a rat insulin radioimmunoassay kit (DiaSorin, Saluggia, Italy) in a gamma counter (LKB, Finland). The plasma total cholesterol and triglyceride concentrations were determined by enzymatic method using diagnostic kits (Rifai *et al.*, 1999). Urea and creatinine in the serum were estimated by using the diagnostic kit based on the method of Thomas (1998).

Uric acid in the plasma was measured estimated by using the diagnostic kit based on the enzymatic method described by Fossati *et al.* (1980). The activities of serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were assayed by using commercially available kits by the method of Moss and Henderson (1999). All assays were carried out in triplicates using a T80 UV-vis Spectrophotometer (PG instrument Ltd., England).

Statistical analysis: Statistical analyses were carried out by SPSS 10 (SPSS, Chicago, Ill) program for windows. Data were expressed as Mean±SEM. Statistical analysis was performed using one-way analysis of variance followed by Tukey post hoc test. The criterion for statistical significance was $p < 0.05$.

RESULTS

There was a significant elevation in serum glucose, total cholesterol, triglycerides, urea, uric acid, creatinine, AST and ALT while the serum insulin level significantly decreased in the diabetic control rats as compared with non-diabetic control group.

As shown in Table 1, diabetic control rats showed a significant reduction in weight gain as compared with the

control animals. Treatment with *Salvia verticillata* extract or glibenclamide caused slight but significant increase in the weight gain in the body weight of these animals.

Figure 1a and b showed the levels of serum glucose and insulin of normal and experimental animals. There was a significant elevation in serum glucose while the level of insulin decreased in the diabetic animals. The effect of administration of *Salvia verticillata* extract at 0.05, 0.1 and 0.2 g kg⁻¹ b.wt. and glibenclamide tended to bring the parameters significantly towards normal values. The effect of *Salvia verticillata* extract was similar to that observed for glibenclamide. The administration of extract (0.05, 0.1 and 0.2 g kg⁻¹ b.wt.) did not change serum glucose and insulin levels in normal rats.

Figure 2a and b showed the levels of serum triglycerides and total cholesterol of normal and experimental animals. There was a significant elevation in serum triglycerides and total cholesterol in the diabetic animals. The effect of administration of *Salvia verticillata* extract at 0.05, 0.1 and 0.2 g kg⁻¹ b.wt. and glibenclamide tended to bring the parameters significantly towards normal values. The effect of *Salvia verticillata* extract was similar to that observed for glibenclamide. The administration of extract (0.05, 0.1 and 0.2 g kg⁻¹ b.wt.) did not change serum triglycerides and total cholesterol levels in normal rats.

Table 1: Changes in the body weight in nondiabetic and diabetic rats after administration with different doses of *Salvia verticillata* extract for 14 days

Stage	Non diabetic rats			Diabetic rats				Glibenclamide	
	Control (distilled water)	Extract (g kg ⁻¹)			Control (distilled water)	Extract (g kg ⁻¹)			
		0.05	0.1	0.2		0.05	0.1	0.2	
Initial (g)	212±11.5	224±15.1	206±7.1	202±12.1	218±13.4	223±17.4	226±10.3	219±11.5	224±13.4
Final (g)	243±10.8	238±10.7	241±12.3	245±14.3	168±11.5*	183±15.4	198±12.7*	205±15.8**	209±12.8***

Values are Mean±SEM. of 8 rats. * $p < 0.05$ different from nondiabetic control rats. * $p < 0.05$ different from diabetic control rats. ** $p < 0.01$ different from diabetic control rats. *** $p < 0.001$ different from diabetic control rats

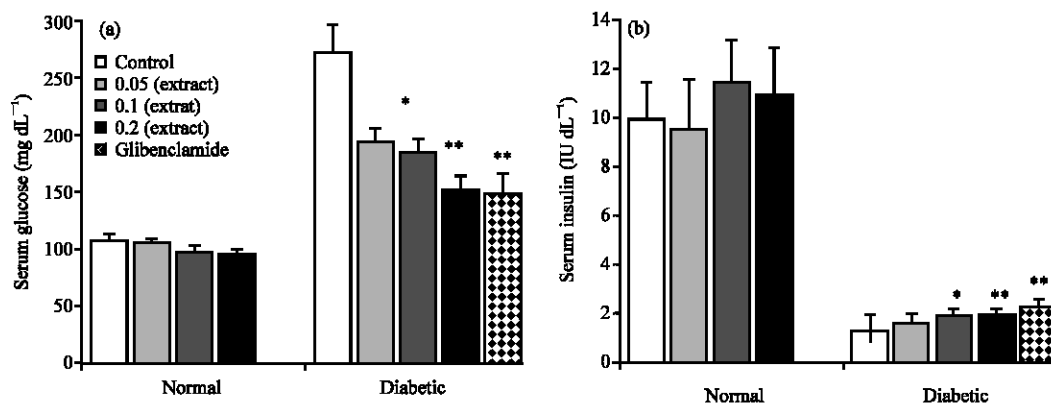


Fig. 1: Effect of oral administration of *Salvia verticillata* aerial parts ethanolic extract at doses of 0.05, 0.1 and 0.2 g kg⁻¹ b.wt. on (a) serum glucose and (b) insulin levels in normal and diabetic rats. Glibenclamide (600 µg kg⁻¹) was administrated only diabetic rats. Each column represents Mean±SEM for 8 rats. Control group administrated with distilled water as a vehicle. * $p < 0.05$, ** $p < 0.01$ different from control diabetic group

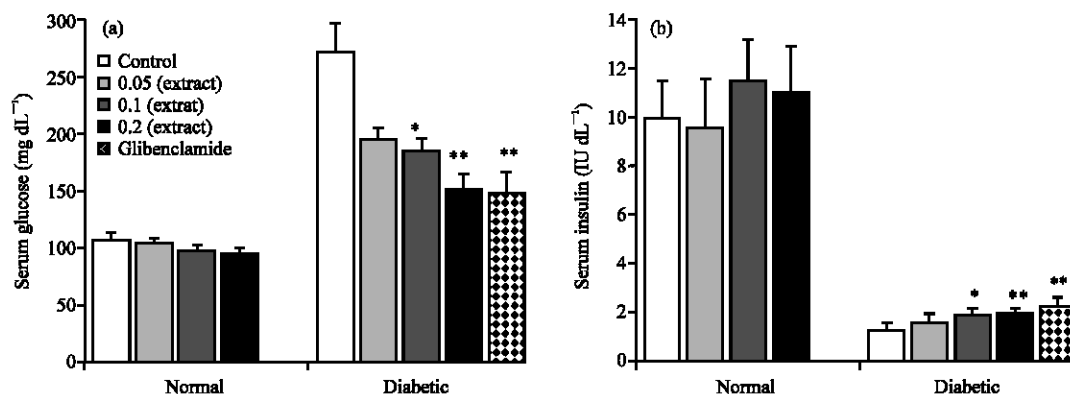


Fig. 2: Effect of oral administration of *Salvia verticillata* aerial parts ethanolic extract at doses of 0.05, 0.1 and 0.2 g kg⁻¹ b.wt. on (a) serum triglycerides and (b) total cholesterol levels in normal and diabetic rats. Glibenclamide (600 µg kg⁻¹) was administrated only diabetic rats. Each column represents Mean±SEM for 8 rats. Control group administrated with distilled water as a vehicle. *p<0.05, **p<0.01, ***p<0.001 different from control diabetic group

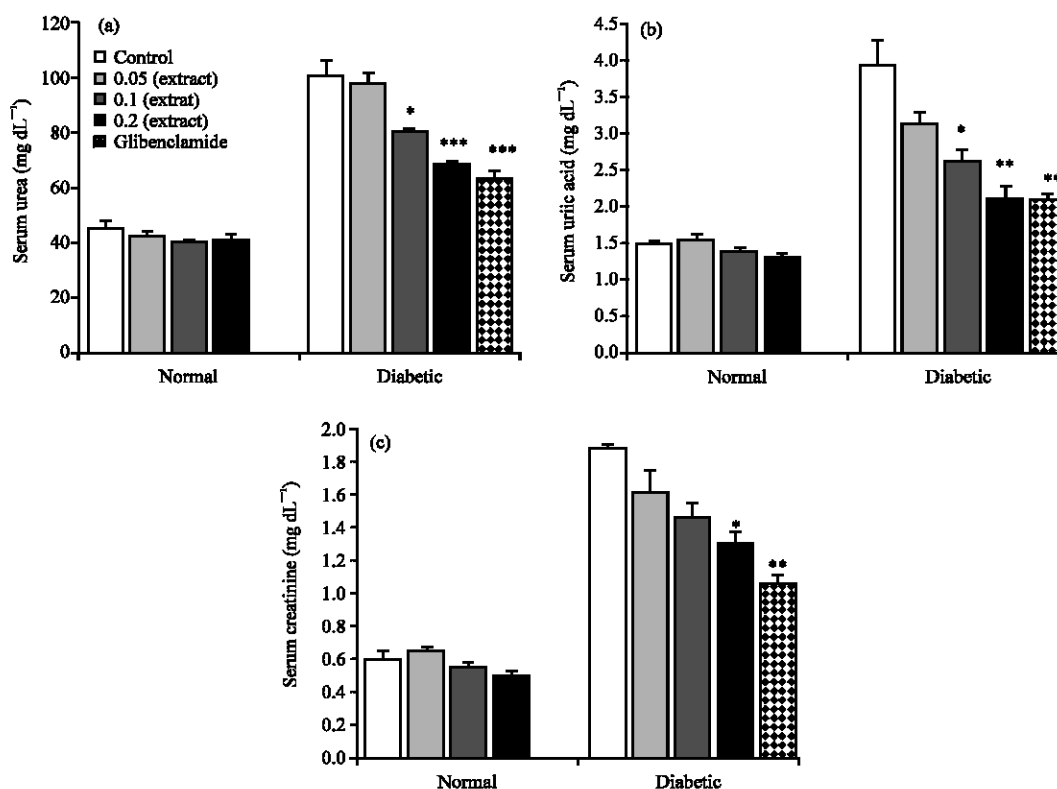


Fig. 3: Effect of oral administration of *Salvia verticillata* aerial parts ethanolic extract at doses of 0.05, 0.1 and 0.2 g kg⁻¹ b.wt. on (a) serum urea, (b) uric acid and (c) creatinine levels in normal and diabetic rats. Glibenclamide (600 µg kg⁻¹) was administrated only diabetic rats. Each column represents Mean±SEM for 8 rats. Control group administrated with distilled water as a vehicle. *p<0.05, **p<0.01, ***p<0.001 different from control diabetic group

Figure 3a-c showed the levels of serum urea, uric acid and creatinine of normal and experimental animals.

There was a significant elevation in serum urea, uric acid and creatinine in the diabetic animals. The effect of

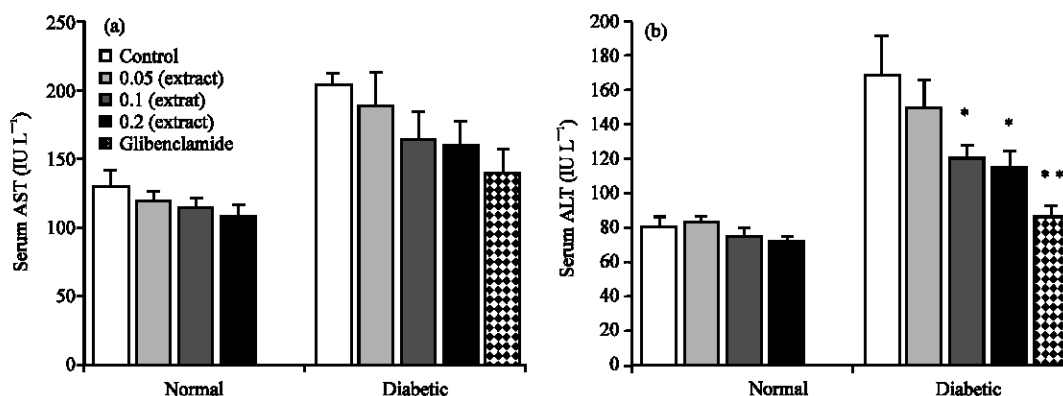


Fig. 4: Effect of oral administration of *Salvia verticillata* aerial parts ethanolic extract at doses of 0.05, 0.1 and 0.2 g kg⁻¹ b.wt. on (a) serum AST and (b) ALT levels in normal and diabetic rats. Glibenclamide (600 µg kg⁻¹) was administered only diabetic rats. Each column represents Mean±SEM for 8 rats. Control group administrated distilled water as a vehicle. *p<0.05, **p<0.01 different from control diabetic group

administration of *Salvia verticillata* extract at 0.05, 0.1 and 0.2 g kg⁻¹ b.wt. and glibenclamide tended to bring the parameters significantly towards normal values. The effect of *Salvia verticillata* extract was similar to that observed for glibenclamide. The administration of extract (0.05, 0.1 and 0.2 g kg⁻¹ b.wt.) did not change serum urea, uric acid and creatinine levels in normal rats.

Figure 4a and b showed the levels of serum ALT and AST of normal and experimental animals. There was a significant elevation in serum ALT and AST in the diabetic animals. The effect of administration of *Salvia verticillata* extract at 0.05, 0.1 and 0.2 g kg⁻¹ b.wt. and glibenclamide tended to bring the parameters significantly towards normal values. The effect of *Salvia verticillata* extract was similar to that observed for glibenclamide. The administration of extract (0.05, 0.1 and 0.2 g kg⁻¹ b.wt.) did not change serum ALT and AST levels in normal rats.

DISCUSSION

The present results showed that the *Salvia verticillata* ethanolic significantly decreased serum glucose, triglycerides, cholesterol, urea, uric acid, AST and ALT whereas it increased serum insulin levels in treated diabetic rats as compared with control diabetic rats.

Models of experimental diabetes that utilizes diabetogenic agents (alloxan and STZ) and induced blood glucose levels higher than 300 mg dL⁻¹ (Sharma *et al.*, 2003) or 400 mg dL⁻¹ (Grover *et al.*, 2000) have been considered as severe diabetes. In our study, as observed from the values of parameters known to suffer changes in this illness, the STZ-induced diabetic rats presented clear symptoms of severe diabetes in the

diabetic control group. The induction of diabetes by an intraperitoneal injection of STZ (70 mg kg⁻¹ wt.) was confirmed, as reflected by the hyperglycemia (serum glucose = 300 mg dL⁻¹), polyphagia, polydipsia and body weight loss compared to the nondiabetic control rats. STZ-induced diabetes is characterized by severe loss in body weight and the loss may be due to degradation of structural proteins since structural proteins are known to contribute to the body weight. In our study, weight loss was observed and treatment with *Salvia verticillata* extract reversed the weight loss, which may be due to increased secretion of insulin by *Salvia verticillata* extract. Treatment with *Salvia verticillata* extract and glibenclamide showed the reversal of serum glucose to near normal level which is supported by the elevated level of plasma insulin. The elevated insulin in *Salvia verticillata* extract treatment could be due to increased secretion by regenerated β-cells.

Dyslipidemia, is a frequent complication noted in chemical-induced diabetes (Luo *et al.*, 2004; Maiti *et al.*, 2005; Umesh *et al.*, 2005) and present a serious risk of vascular disease. The total cholesterol and triglycerides of the diabetic animals treated with extract was substantially improved, as compared to diabetic control group. This suggests that the strong anti-hyperglycemic effect of extract could indirectly be related to beneficial action against the abnormal high concentration of serum lipids observed in diabetes animals. Literature has shown flavonoids, alkaloids to be the active hypoglycemic principle in many medicinal plants with blood glucose and lipids-lowering attributes (Oladele *et al.*, 1995). The presence of flavonoids, terpenoids and Rosmarinic acid in the plant were reported (Nagy *et al.*, 1999; Sonmez *et al.*, 1997), may account for the observed antidiabetic effects of the extract.

The diabetic hyperglycemia induces elevation of serum levels of urea, uric acid and creatinine which are considered as significant markers of renal dysfunction (Shinde and Goyal, 2003). The results showed significant increase in the level of serum urea, uric acid and creatinine in the diabetic groups. These results indicated that diabetes could be lead to renal dysfunction. While, after treatments of diabetic rats with extract or glibenclamide, the level of these parameters were significantly decreased in serum compared to the mean value of diabetic group.

The liver is the most important organ for regulating glucose metabolism by assimilating increased blood glucose in the form of glycogen and/or regulating the new synthesis of glucose through gluconeogenesis (Yoon *et al.*, 2001). Enzymes directly associated with the conversion of amino acids to keto acids are ALT and AST. ALT and AST activities are used as the indicators of hepatocyte damage (Whitehead *et al.*, 1999). The increase in the activities of serum AST and ALT indicated that diabetes may be induced hepatic dysfunction. Therefore, the increment of the activities of AST and ALT in serum may be mainly due to the leakage of these enzymes from the liver cytosol into the blood stream (Navarro *et al.*, 1993), which gives an indication on the hepatotoxic effect of alloxan. Diabetic rats have increased activities of these enzymes which may be due to hepatic damage and treatment with *Salvia verticillata* extract has decreased the activities of these enzymes, by its antioxidant properties (Ramesh and Pugalendi, 2006). On the other hand, treatment of the diabetic rats with either extract or glibenclamide caused reduction in the activity of these enzymes in serum compared to the mean values of diabetic group. A possible explanation for the differential effects of the plant extract on the activities of AST and ALT in serum is that these treatments may inhibit the liver damage induced by STZ.

Salvia verticillata L. contains a variety of polyphenols (rosmarinic acid being the most representative), volatile oils and diterpenoids (Krstic *et al.*, 2006; Tepe *et al.*, 2006; Nagy *et al.*, 1999). It is reported that rosmarinic acid and its derivatives are more likely to be responsible for most of the observed antioxidant activities of *Salvia* species. Rosmarinic acid is the predominant phenolic compound in *Salvia verticillata* L. (Lima *et al.*, 2005). Luteolin-7-glucoside, the major flavonoid present in the plant and also monoterpenes present in the essential oil fraction, could, on the other hand, be good candidates. However, pre-treatment of rats with luteolin-7-glucoside was recently found to protect significantly against CCl₄-induced toxicity and its effects attributed to the

compound's antioxidant properties acting as scavenger of reactive oxygen species (Zheng *et al.*, 2004). A number of investigators have shown that flavonoids, tannins and other polyphenolic compounds (e.g., coumarins), triterpenoids and a host of other secondary plant metabolites possess hypoglycaemic and antihypertensive properties in various experimental animal models (Marles and Farnsworth, 1995; Akah and Okafor, 1992). Most likely, the ethanolic extract effects observed here was a result of interactions and synergisms among the different compounds and metabolites present, which makes it difficult to attribute them to any particular compound or family of compounds.

CONCLUSIONS

These results support the acceptance of the null hypothesis that there is no significant difference between the plant extract in comparison to glibenclamide (=standard antidiabetic drug). Finally, although the present data do not clearly indicate the mechanism of action, the strong antidiabetic effect observed in STZ-induced diabetic rats justifies the use of *Salvia verticillata* for the treatment of diabetes-related complications.

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