Evaluation of Hypoglycemic Activity of *Salvia officinalis L.* (Sage) Infusion on Streptozotocin-Induced Diabetic Rats

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Abstract: *Salvia officinalis* L. (sage) is reported to have a wide range of biological activities and possess hypoglycemic effects in diabetic animals. The aim of this study was to evaluate the possible curative role of sage using streptozotocin (STZ)-induced diabetic rats. The animals were rendered diabetic by a single intraperitoneal (i.p.) injection of 50 mg/kg STZ. Blood samples were obtained from retro-orbital sinus after four weeks from oral administration of sage tea. The results showed that i.p. injection with STZ induced very highly significant elevation in blood glucose concentration as compared with control group. Diabetic rats also revealed highly significant elevation in lipid peroxide (MDA) level, total cholesterol (TC), triacylglycerols (TAG), low-density lipoprotein cholesterol (LDL-C) and very low-density lipoprotein cholesterol (VLDL-C) concurrent with highly significant reduction in high-density lipoprotein cholesterol (HDL-C) as compared with control group. Injection of sage tea had no effect on normal rats. Meanwhile, treatment with sage to diabetic rats induced significant improvement in all tested parameters, it reduced significantly blood glucose and MDA levels, as well as induced significantly amelioration in lipid profile parameters as compared with non treated diabetic group. Therefore, it could be concluded that sage had a potent hypoglycemic activity, this effect may be attributed to its antioxidant activities.
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Key words: *Salvia officinalis* (sage), diabetic rats, lipid profile, malondialdehyde (MDA).

1. Introduction

Diabetes mellitus is one of the most common endocrine metabolic disorders, characterized by hyperglycemia due to defects in insulin secretion, action or both **(Ayyanar *et al.*, 2008 and Hajzadeh *et al.*, 2011**), it has caused a significant morbidity and mortality due to microvascular (retinopathy, neuropathy and nephropathy) and macrovascular (heart attack, stroke and peripheral vascular disease) complications **(Patel *et al.*, 2011a)**. Human bodies possess enzymatic and non-enzymatic antioxidant mechanisms which minimize the generation of reactive oxygen species, responsible for many degenerative diseases including diabetes **(Patel *et al.*, 2011b)**. The world prevalence of diabetes among adults expected to be 7.7% affecting 439 million adults by year 2030 **(Shaw *et al.*, 2010).**

Currently available therapies for diabetes, include insulin and various oral anti-diabetic agents, are expensive and not easily accessible. Presently, there is growing interest in herbal remedies due to the side effects associated with the oral hypoglycemic agents (therapeutic agent) used for the treatment of diabetes mellitus. In recent years, herbal medicines have to gain importance as a source of hypoglycemic agents in order to provide a scientific explanation for their beneficial effect **(Patel and Srinivasan, 1997 and Rao *et al.*, 2010).** Herbal medicines known to be useful in diabetes treatment (**Samane *et al.*, 2006**). Today plant-based medicines play a key role in the healthcare systems of the developing countries, where modern drugs are not usually affordable **(Sah *et al.*, 2011)**. The massive use of plants is encouraged by their efficiency, availability, and the low cost of herbal **(Akomo *et al.*, 2009).**

Plant constitutes consider important sources of active natural products which differ widely in terms of structures, biological properties and mechanisms of actions, various phytochemical components, especially polyphenols (such as flavonoids, phyenyl propanoids, phenolic acids, tannins, etc) are known to be responsible for the free radical scavenging, inhibition of peroxidantion, chelating transition metals and antioxidant activities of plants **(Lee *et al.*, 2003 and Melo *et al.*, 2005).** In recent years, the extracts of many plants have been screened for their antioxidant and hypoglycemic activities. Among these, sage is well-known for their antioxidant properties and most of its active components have been identified. It has been established that the antioxidant effects are mainly due to the phenolic compounds of the plant (**Bandoniene *et al.*, 2002, Miura *et al.*, 2002 and Tepe *et al.*, 2006).**

Salvia officinalis L. (sage), a member of the family of Lamiaceae, has been reported to have wide range of biological activities. It has been proposed as effective against cardiovascular diseases, brain and nervous disorders, various infections (such as throat infections, dental abscesses, and mouth ulcers) and

digestion problems **(Stephan *et al.*, 2012).** Sage is among the plants that are claimed to be beneficial to diabetic patients. **Lima *et al.* (2006)** showed that a sage methanolic extract given intraperitoneally significantly reduced serum glucose level in fasted streptozotocin - induced diabetic rats without change in insulin level. **Amin and Hamza (2005) and Carla *et al.* (2009)** reported that sage (*Salvia officinalis L.*) reducing malonialdehyde level and releasing the inhibitory effect of azathioprine on the activities of glutathione, catalase and superoxide dismutase enzymes. In addition, **Lima *et al.* (2005)** demonstrated that the replacement of drinking water with sage tea in rats resulted in an improvement of the antioxidant status of rat. Therefore, the purpose of the current study was to examine the hypoglycemic effects of oral administration of sage infusion on diabetic male rats.

2. Material and methods:

Material:

Plant material

Leaves and branches of sage plant (*Salvia officinalis L.*), family Labiatae (*Lamiaceae*) were obtained from Prof. Dr. E.A. El- Ghadban, Professor of Medicinal and Aromatic Plants, Medicinal and Aromatic Plants Research department, Horticultural Research Institute, Agricultural Research Center. The herbs wad identified by Dr. Mohamed A. El-Gibali, Senior Botanist, Department of Pharmacognosy, Faculty of Pharmacy, Cairo University Giza, Egypt. The plant was dried at 30-40 ºC by the hybrid solar convective drying system, belonging to the Solar Energy Dept., National Research Center, Dokki, Egypt.

Drugs and Chemicals

Streptozotocin (STZ) was purchased from Sigma Chemical Co. (St Louis, Mo, USA). Starch and corn oil were obtained from local market. Casein, vitamins, minerals, sucrose and cellulose were obtained from El-Gomhoriya Pharm. and Chem. Ind. Co. Cairo, Egypt. The kits used for determination of serum biochemical parameters were purchased from Alkan Pharm. Ind. Co. Cairo, Egypt.

Methods:

Preparation of sage tea:

Considering the sage is traditionally used as a tea, an infusion of sage tea was freshly prepared by pouring 150 ml of boiling water onto 2 g dried plant material, covering and allowing it to steep for 5 min according to **Lima *et al.* (2005).**

Experimental animals:

Twenty four adult male albino rats of *Sprague Dawely* strain, weighing (180 ± 10 gm) were used for this study. They were kept for one week for proper acclimatization before starting the experiment under the same controlled laboratory conditions of illumination (12h light/12h darkness), temperature 20-25°C and ventilation. They were housed in stainless steel cages, maintained on standard casein diet **(Reeves *et al.*, 1993)** (14% casein, 10 % sucrose, 5% corn oil, 5% fiber (cellulose), 3.5% mineral mixture, 1 % vitamin mixture, 0.3 % D-L methionine , 2.5 % choline chloride and the remainder is corn starch) and water or sage tea *ad libitum* throughout the experimental period.

Induction of diabetes:

Diabetes was experimentally induced by using a single intraperitoneal (i.p.) injection of 50 mg/kg body weight STZ dissolved in 0.2 ml of 0.05 M citrate buffer pH: 4.5 according to (**Lutz and Pardridge, 1993).** Diabetic rats were supplied with 5% sucrose solution orally for the first 48 hrs, after STZ injection to minimize death from hypoglycemia **(Peschke *et al.*, 2000).** Seventy-two hrs. later, blood samples were obtained by puncture of retro-orbital plexus with a fine capillary glass tube and blood glucose concentrations were determined to confirm induction of diabetes. Animals with blood glucose levels > 300 mg/dl were considered diabetic and used for the experiment.

Experimental design:

After acclimatization period, rats were randomly divided into four groups, each of six rats as follows:

Group 1: Control group, rats i.p. injected with 0.2 ml of 0.05 M citrate buffer pH: 4.5 (negative control), rats were given standard diet and tap water *ad libitum*.

Group 2: Diabetic rats, injected i.p. with 50 mg/kg body weight STZ, and given standard diet and tap water *ad libitum*.

Group 3: Sage group, rats i.p. injected with the same method as in group (1), 72 hrs, later they received sage tea *ad libitum* as a replacement for their water (beverage was renewed daily).

Group 4: Diabetic rats as in group (2), 72 hrs, later they treated with sage at the same route as in group (3).

The experiment lasted for four weeks starting from sage administration. At the end of the experimental period, rats were deprived of food overnight and sacrificed under ether anesthesia. At the end of the experimental period, the rats were anaesthetized with diethyl ether. Blood samples were collected by puncture of retro-orbital plexus with a fine capillary glass tube. Collected blood was stored for 30 min at room temperature and centrifuged with 3000 rpm for 15 min. The supernatant kept in - 20 ºC until use.

Biochemical analysis:

Separated serum samples were used for determination of glucose enzymatically **(Trinder, 1969)**, malondialdehyde (MDA) **(Yoshioka *et al.*, 1979)**, total cholesterol (TC) **(Allain *et al.*, 1974)**, high density lipoprotein cholesterol (HDL-C) **(Demacker *et al.*, 1980)** and triacylglycerols (TAG) **(Fossati and Prencipe, 1982).**While low-density lipoprotein

cholesterol (LDL-C) and very low-density lipoprotein cholesterol (VLDL-C) were calculated according to the equation of **(Friedwald *et al.*, 1972)**.

Statistical analysis:

Results were expressed as mean ± SE. Data were statistically analyzed for variance and the least significant difference (LSD) using one way analysis of variance (ANOVA) according to **(Snedecor and Cochron, 1989)**. An IBM computer with a software system SPSS version 20 was used for these calculations.

3. Results and Discussion:

Diabetes Mellitus is a metabolic disorder characterized by hyperglycemia, chronic hyperglycemia in diabetes is associated with long term damages, dysfunction and eventually the failure of organs, especially the eyes, kidneys, nerves and cardiovascular system **(Vinik and Vinik , 2003)**. Sage (*Salvia officinalis* L.) has a wide range of biological activities, such as antioxidative properties, anti-bacterial, hypoglycemic, anti-inflammatory, fungistatic, virustatic, astringent, eupeptic and anti-hydrotic effects **(Eidi and Eidi, 2009)**

Effect of aqueous extracts of sage on serum levels of glucose concentration and malondialdehyde (MDA) in diabetic rats is presented in Table (1). Results showed that, the glucose level revealed marked very highly significant elevation (p <0.001) in diabetic rats by 207.65% when compared to non diabetic group. These findings agree with those reported by **Daisy *et al.* (2010)** who found that the diabetogenic agent streptozotocin destruct β-cells of the islets of Langerhans in the pancreas, which result in inhibition of insulin synthesis and elevation of blood glucose level, firstly due to reduction in entry of glucose to peripheral tissues, muscle and adipose tissue, and secondly to increased glycogen breakdown and increased gluconeogenesis and hepatic glucose production. **Mahesh *et al.* (2010)** reported that administration of STZ caused impaired glucose-stimulated insulin release and insulin resistance which may be attributed to destruction of pancreatic β-cells in rats. The possible mechanisms for β-cells destruction by STZ due to induce generation of some types of oxygen free radicals and alteration of endogenous scavengers of these reactive species, fragmentation of DNA and the subsequent increase in the activity of poly-ADP ribose synthase (an enzyme known to deplete nicotinamide adenine dinucleotide in β-cells), inhibition of ATP synthesis and islet mitochondria l respiratory enzymes **(Ohkuwa *et al.*, 1995).**

Oral administration of sage tea to normal rats had no effect on glucose concentration, their values tended to match with the control value, indicating its safe use under the experimental conditions, while treatment with sage to diabetic rats significantly (p<0.001) ameliorated the elevation in glucose concentration (the percent change as compared to non-treated diabetic rats was 59.7%).

The obtained result was similar to these obtained by **Eidi and Eidi (2009)** who reported that oral administration of 0.2 and 0.4 g/kg body wt. of the sage extract for 14 days exhibited a significant reduction in serum glucose, triglycerides, total cholesterol, urea, uric acid, creatinine, AST, ALT and increased plasma insulin in streptozotocin-induced diabetic rats but not in normal rats. The hypoglycemic effect may be attributed to increase the hepatocyte glucose consumption, decrease fasting gluconeogenesis and inhibit the stimulation of hepatic glucose production by glucagon **(Eidi *et al.*, 2005 and Lima *et al.*, 2006)**.

The current study elicited marked significant elevation (p<0.001) in the lipid peroxidation product (MDA) level in diabetic group by 49.5% as compared with control group, this is an indicator of free radical generation. These findings agree with that of **Lu and Foo (2001).** Concerning normal rats received oral administration of sage the results showed non-significant difference in MDA level compared with control rats. On the other hand, diabetic rats treated orally by sage showed significantly (p<0.001) improvement in MDA level as compared with diabetic non treated group. Consistent with the present study **Luvone *et al.* (2006) and Elida *et al.* (2010)** reported that sage modulated antioxidant pathways to minimize stress by scavenging free radicals. This may be due to the active constitutes of sage polyphenols, especially, phenolic and rosmarinic acid in sage which has potent antioxidant effect, thus protecting membrane lipids of fatty acids and phospholipids from oxidative stress (**Lima *et al.*, 2005, Nour *et al.*, 2010 and Kianbakht *et al.*, 2011**).

Table (1): Effect of sage tea treatment on serum glucose and lipid peroxide as malondialdehyde (MDA) concentration in normal and diabetic rats.

Experimental Groups / Parameters	Control	Diabetic	Sage	Diabetic + sage
Glucose (mg/dl)	98. 94 ± 4.31	304.39 ± 16.63 ^{a***}	96.39 ± 4.79	122.53 ± 5.22 ^{b***}
MDA (nmol/l))	74. 29 ± 1.73	111.07 ± 3.29 ^{a***}	71. 53 ± 1.28	80. 19 ± 1.29 ^{b***}

- Each value represents the mean of 6 rats ± SE.

- [a] Significant difference from control group at $p < 0.05$*, highly significant difference at $p < 0.01$** and very highly significant difference at $p < 0.001$*** from control group.
- [b] Significant difference between diabetic group and diabetic group treated with sage at $p < 0.05$*, highly significant difference at $p < 0.01$** and very highly significant difference at $p < 0.001$***.

Table (2): Effect of sage tea treatment on serum lipid profile parameters in normal and diabetic rats.

Experimental Groups / Parameters	Control	Diabetic	Sage	Diabetic + Sage
TC (mg/dl)	90.94 ± 2.32	149.92 ± 6.72 [a***]	87.77 ± 1.88	98. 72 ± 4.78 [b***]
TAG (mg/dl)	85.20 ± 1.19	135.49 ± 9.02 [a***]	83.46 ± 1.12	92.68 ± 2.09 [b***]
HDL-C (mg/dl)	44.12 ± 1.38	32.37 ± 1.24 [a***]	46.20 ± 1.01	40.29 ± 1.84 [b***]
LDL-C (mg/dl)	17.04 ± 0.24	27.10 ± 0.22 [a***]	16.69 ± 0.22	18.54 ±0.42 [b***]
VLDL-C (mg/dl)	29.78 ± 1.96	90.45 ± 5.70 [a***]	24.88 ± 1.98	39. 89 ± 2.82 [b***]

- Each value represents the mean of 6 rats ± SE.
- [a] Significant difference from control group at $p < 0.05$*, highly significant difference at $p < 0.01$** and very highly significant difference at $p < 0.001$*** from control group.
- [b] Significant difference between diabetic group and diabetic group treated with sage at $p < 0.05$*, highly significant difference at $p < 0.01$** and very highly significant difference at $p < 0.001$***.

Data illustrated in Table (2) revealed the effect of oral administration of sage tea treatment on serum lipid profile parameters in normal and diabetic rats. Diabetic rats showed significant elevation ($p < 0.001$) in TC, TAG, LDL-C and VLDL-C by 64.9%, 59.02%, 59.03% and 203.7% respectively concurrent with significant reduction in HDL-C ($p < 0.001$) as compared with control negative group by 26.6% .The present results are in agreement with that of **Mooradian (2009)** who reported that defects in insulin action and hyperglycemia could lead to these changes, the characteristic features of diabetic dyslipidemia are a high triglyceride concentration, low HDL-C concentration and increased concentration of LDL-C particles.

Normal rats received sage tea showed no significant changes in these parameters compared with control rats, meanwhile diabetic rats treated with oral administration of sage exhibited significant decrease in TC, TAG, LDL-C and VLDL-C by 49.35%, 31.59%, 31.58% and 33.94%, respectively. On the other hand a significant increase was observed in HDL-C by 24.46% when compared with non treated diabetic group ($p< 0.001$). Similar results were obtained by **Carla *et al.* (2009)** and **Kianbakht *et al.* (2011)** who reported that *Salvia officinalis* tea consumption is accountable for the improvement of the lipid profile inducing a decrease on the highly atherogenic LDL-C particles (which are easily oxidable and less readily cleared) and an increase in the HDL-C, these effect may be due to the ability of *Salvia officinalis* to suppress cholesterol biosynthesis **(Akram and Maryam, 2009 and Moram, 2001).** Moreover, **Ninomiya *et al.* (2004)** demonstrated that *Salvia officinalis* L. leaves methanolic extract have a significant inhibitory effect on serum triglyceride elevation. However, sage modulating results may attributed to several sage natural components that have been shown to act on cholesterol metabolism by reducing its absorption or its synthesis, such as catechins **Plana *et al.* (2008).** Thujone is a monoterpene that occurs mainly as a mixture of alpha and β diastereoisomers in many plants such as *Artemisia absinthium* L. and *Salvia officinalis* L., it lowers cholesterol and triglyceride levels **(Kee *et al.*, 2009 and EL-Kholy *et al.*, 2010).**

In conclusion, oral administered of *Salvia officinalis* revealed significant hypoglycemic activity in STZ-induced diabetic rats. This effect may be attributed to its antioxidant activity and its high content of polyphenols. Therefore, it could be recommended that sage tea should be ingested to diabetic and hypercholesterolemic patients beside the usual therapy. Further analytical studies of the substances in sage tea should be carried out to complete the profile of the plant in order to introduce it as a natural antidiabetic agent.

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