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Hypoglycemic and hypolipidemic activities of *Salvia hydrangea* in streptozotocin-induced diabetes in rats

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ABSTRACT

Objective(s): This study was to investigate the potential anti-diabetic effects of alcoholic extract of *Salvia hydrangea* in rats.

Materials and Methods: Thirty five male Wistar rats were divided into five groups namely non-diabetic control, diabetic control, and three experimental diabetic that received either *Salvia hydrangea* extract for 21 days at the doses of 100 and 200 or glibenclamide at the dose of 10 mg/kg through gavage feeding. To induce diabetes, streptozotocin was injected intraperitoneally.

Results: Insulin and HDL levels in the group receiving the high dose of the extract showed significant increase, whereas the amount of cholesterol in rats that received glibenclamide and the extract showed a significant decrease as compared to the diabetic control group *(P*<0.05*).* The blood glucose levels showed significant reduction in all experimental groups *(P*<0.05*).*

Conclusion: Consumption of the extract of the aerial parts of *S. hydrangea* which reduces blood fat and increases insulin may have beneficial effects on the symptoms of diabetes and hyperlipidemia.

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Introduction

Diabetes mellitus is a systemic metabolic disease characterized by hyperglycemia, hyperlipidemia, and decreased insulin secretion or function and is often associated with small and large vessel diseases like neuropathy, nephropathy, cardiovascular and cerebrovascular diseases. Diabetes mellitus is associated with prolonged hyperglycemia which is an important factor in the development of the above-mentioned diseases (1).

Currently, diabetes is developing rapidly throughout the world. As estimated by the World Health Organization, the number of people with diabetes, in 2025, will amount to nearly 300 million people (2). Patients are commonly treated by insulin and anti-diabetic agents such as glibenclamide, gliclazide and metformin. These drugs act through increasing insulin secretion from pancreatic beta cells, increasing tissue sensitivity to insulin and also inhibiting intestinal absorption of sugars. However, some of these medications have side effects such as drug tolerance, disease progression despite medication, headache, megaloblastic anemia, dermatitis, acidosis caused by lactic acid, etc. Therefore, seeking safer and healthier hypoglycemic agents is of utmost importance (3).

Natural products which have anti-diabetic potential act through their insulino-mimetic properties, inhibition of intestinal absorption of glucose, or insulin dependent metabolic processes. Herbal products have long been used to cure diabetes. Ethnobotanical studies show that more than 100 species of plants have anti-diabetic activity (1). Naturally occurring compounds like alkaloids, peptidoglycan, terpenoids, amino acids and inorganic ions have hypoglycemic properties. Different species of Salvia have been used in traditional medicine to treat diabetes. Members of the genus Salvia have significant biological and pharmacological properties e.g. astringent, antiseptic and spasmolytic effects.

In Iranian traditional medicine *Salvia Mirzayanii* (locally known as Bitter Moor) has been used for stomach pains and the flowers of *Salvia hydrangea* (locally known as Gol-e Arooneh) have been used to treat colds (4, 5). Salvia genera are generally called *Salvia officinalis*, which are the largest subdivisionof Lamiaceae family. There are about 58 species in this genus, 17 of which are native plants of Iran.

Salvia species are also rich in phenolic flavonoids and phenolic acids (4). Many of these species and

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their compounds have significant antioxidant properties which act through enzymatic and non-enzymatic pathways (5). Alpha-amylase is one of the key enzymes in human responsible for the breakdown of starch into simple sugars. Inhibition of this enzyme can inhibit carbohydrate digestion and cut glucose absorption rate. Various species of *S. hydrangea* reduce the activity of this enzyme (6).

Genus Salvia is also rich in terpenoids. *S. hydrangea* grows widely in Fars province of Iran and in traditional medicine it has been used as an anti-inflammatory, analgesic, and antispasmodic remedy. Three isoterpenoids namely Salvadione C, Perovskone B and Hydrangenone have been recently isolated from *S. hydrangea* (7). Studies indicate that terpenoids are useful in treating diabetes (1).

The main objective of this research was to study the effects of alcoholic extract of *S. hydrangea* on lipid and glucose profiles in streptozotocin (STZ)-induced diabetes in rats.

Materials and Methods

Animals

The present study was carried out in 35 male Wistar rats (200-250 g). The rats were housed under temperature and humidity-controlled condition with a 12 hr: 12 hr light-dark cycle. The entire process was in compliance with the codes of ethics and guidelines for working with laboratory animals approved by the Islamic Republic of Iran Ministry of Health and Medical Education (MOHME).

Experimental groups

The rats were randomly divided into 5 groups (n=7), as follows:

1- Non-diabetic control group only received normal diet and water. 2- Diabetic control group received 1 ml of normal saline daily as extract solvent. 3- Diabetic rats treated with alcoholic extract of *S. hydrangea* (100 mg/kg) 4 - Diabetic rats treated with alcoholic extract of *S. hydrangea* (200 mg/kg), 5 - Diabetic rats treated with glibenclamide (10 mg/kg).

Induction of diabetes

Twelve hours before administration of streptozotocin (STZ) (Upjohn Company, USA), animals were kept hungry with free access to water. For induction of diabetes, STZ was dissolved in normal saline. A single dose (60 mg/kg) of STZ was administered intraperitoneally (IP). After 48 hr, to ensure the induction of diabetes, fasting blood glucose levels were measured with Easy Gluco (Combo 142, USA). Rats with blood sugar levels above 220 mg/dl were considered as diabetic. Diabetic rats showed symptoms of frequent urination and polydipsia. For the next three weeks, on a daily basis, diabetic animals received the above-mentioned doses of the extract and glibenclamide by gavage feeding (8).

All groups were kept fasting overnight before blood sampling while they had free access to water. Blood sugar levels were measured during the first day of testing and the day before diabetes induction (day zero). Also, blood sugar levels were measured and recorded weekly. The experiment lasted for 21 days during which treatments were gavaged regularly at 9 a.m. every day. After this period, rats were mildly anesthetized with ether and blood samples were taken from their heart to check blood glucose, insulin levels and lipid profiles, high-density lipoprotein (HDL), low-density lipoprotein (LDL), triglyceride (TG), and cholesterol. After centrifugation of blood (Mini Spin Eppendorf, Germany) at 3000 rpm for 10 minutes plasma was separated and sent for the measurement of the aforementioned factors.

Extraction method

S. hydrangea grows widely in Fars province (Iran). It has been identified by Sonboli and colleagues and stored with the herbarium code of MPH-761 at the Medicinal Plants and Drug Research Institute of Shahid Beheshti University of Medical Sciences, Tehran, Iran (9).

To prepare the alcoholic extract of *S. hydrangea*, after providing the aerial parts and removing impurities, 600 g of the plant was ground and mixed with ethyl alcohol 90% with a 1:5 ratio. After 24 hr, it was placed on the stirring device. Then, the extraction was leached by the filter paper and funnel. Ethyl alcohol 70% was added to the obtained sediment and was placed on the stirring device for another 24 hr and then was added to the first extract. Then, the whole extract was distilled in the vacuum distillation unit at 60˚C and 70% rotations until the remaining volume was one-fifth of the initial one. The tank was then removed and after cooling down, the extract was decanted for three times, each time with 50 cc of chloroform. The remainder was poured into Petri and dried in an Avon (Finetech, Korea) at 50 ˚C. The obtained extract (about 10 g per 100 g of crushed plant) was mixed with normal saline to obtain different concentrations.

Analytical methods

Serum cholesterol and TG levels were determined by colorimetric method (Darman kav company, Iran). Lipoproteins were measured by a combination of ultra centrifugation and precipitation methods or using Darman kav company kits (Darman kav company, Iran). HDL cholesterol was measured by precipitation method. First, precipitation reagent was added to the serum in order to integrate non lipoprotein HDL compounds. Then, these compounds were precipitated by centrifugation for 10 min. After that, HDL cholesterol was measured by enzymatic methods. LDL

Table 1. The effects of ethanol extract of *Salvia hydrangea* on fasting blood sugar (FBS) and body weight

Group / Parameters	Non-diabetic control	Control	*Salvia hydrangea* (100 mg/kg)	*Salvia hydrangea* (200 mg/kg)	Glibenclamide (10 mg/kg)
FBS Pre-diabetes	70.5±15.3	70.16±12.7	70±14.8	69.7±17.5	69.0±16.7
48 hr after diabetization	70.5±13.6	302.7±71.1*	385.8±115.3	354.2±129.3	302.85±1.1.3
FBS at the end of the first week	72.7±14.6	339.3±72.8*	231.7±116.2 †	326.2±133.5	302.42±76.8 †
FBS at the end of the second week	68.8±19.2	352±80.3*	109.8±74.7 †	166.3±143.2 †	132.6±89.4 †
FBS at the end of the third week	64.7±17	353.3±123.4*	103.8±21 †	163.2±95.1 †	161.14±84.3 †
Weight before the experimental period	179.7±7.35	181±11.93	180±7.9	180±9.35	181±9.61
Weight after the experimental period	248.3±7.5 α	138.00±2.7 αβ	182±10.95 β	175±11.72 β	160±14.5 αβ

* Marks a significant change compared to the non-diabetic control group
† Marks a significant change compared to the diabetic control group
α Marks a significant change compared to the same period before the test
β Marks a significant change of the diabetic group compared to the non-diabetic control group

cholesterol was calculated, according to Fridewald's formula.

Statistical analysis

The means obtained (Mean±SEM) were statistically analyzed using one way ANOVA, Dancan and Tukey, T-test and K related samples. All statistical analyses were performed by SPSS version 17 *(P≤* 0.05*).*

Results

In this experiment, diabetic rats (diabetic control group and three experimental groups under treatment) received STZ 60 mg/kg body weight. Two days after that, blood glucose level significantly increased compared to the non-diabetic control group (Table 1). The results showed no significant differences in blood glucose levels among diabetic control group and experimental groups treated with extract 100 and 200 mg/kg of body weight as well as the group receiving glibenclamide. The results also showed that after three weeks of treatment, blood glucose levels in rats which either received salvia extract (100 and 200 mg/kg) or glibenclamide, had decreased significantly compared to the diabetic control group (*P*<0.05). The results of the statistical tests (Table 2) indicate that cholesterol level in the diabetic control group showed significant increase in comparison with non-diabetic control group. This was significantly lower than the diabetic control group in the experimental group receiving the high dose of the extract (200 mg/kg). Cholesterol level was significantly lower in the group receiving high-dose extract (200 mg/kg) compared to the diabetic control group. Cholesterol levels in the experimental group that received low-dose extract (100 mg/kg) showed a significant increase in comparison with glibenclamide-treated group (*P*=0.008). Insulin levels in the diabetic control group did show significant changes in comparison with non- diabetic control group, but the rate level of insulin in the experimental group receiving high-dose extract (200 mg/kg) showed a significant increase compared to diabetic control group (*P*=0.005). HDL levels in diabetic control group did not show significant changes compared to non-diabetic control group while its level in the group receiving low-dose extract (100 mg/kg) was significantly higher than in diabetic control group and glibenclamide-treated group as well as the group treated with high-dose extract (200 mg/kg) (*P*=0.002). Moreover, LDL level in diabetic control group showed significant increase compared to non-diabetic control group while its level did not show significant changes in any of the experimental groups as compared to diabetic control group. LDL levels in the experimental group receiving low-dose extract (100 mg/kg) as well as the experimental group which received high-dose extract (200 mg/kg) showed a significant increase compared to glibenclamide-treated group (*P*=0.000). TG level in plasma in diabetic control group did not show significant changes compared to non-diabetic control group. Furthermore, TG levels in all experimental groups did not show significant changes compared to diabetic control group. Only in the experimental group receiving low-dose extract (100 mg/kg) a significant decrease was seen as compared to the group receiving high-dose extract (200 mg/kg) (*P*= 0.002).

Table 2. The effects of ethanol extract of *Salvia hydrangea* on lipid profiles and insulin level

Group / Parameters	Non-diabetic control	Diabetic control	*Salvia hydrangea* (100 mg/kg)	*Salvia hydrangea* (200 mg/kg)	Glibenclamide (10 mg/kg)
Insulin (mu/l)	0.56±.13	0.05±.02*	0.70±0.15 †	1.33±0.3 † α β	0.67±.04 †
HDL (mg/dl)	42.25±6.0	47.50±7.9	63.25±4.5 † α	45.00±3.1 β	36.50±2.0
LDL (mg/dl)	23.75±1.7	45.75±5.9*	57.75±5.3 α	45.20±1.6 β	39.75±3.5
Cholesterol (mg/dl)	58.50±8.4	81.00±2.0*	79.75±11.9 α	60.40±4.2 †	56.00±5.8 †
Triglyceride (mg/dl)	52.50±7.8	43.50±2.1	36.40±4.4	65.50±17.2 β	44.50±6.0

* Marks a significant change in diabetic control group compared to the non-diabetic control group
†Marks a significant change in experimental groups compared to the diabetic control group
α Marks a significant change in group receiving the extract as compared to glibenclamide group
β Marks a significant change in groups receiving the extract together

In this study, rats body weights were analyzed in two ways (Table 1). Weights before and after the experimental period were compared with each other. The weights in control group showed a significant increase, which was the sign ofnatural growth during the experimental period (*P*=0.000). When the weights before and after the experiment in diabetic groups (diabetic control group (*P*=0.002) were compared, the group receiving extract 200 mg/kg (*P*=0.002) and the group receiving glibenclamide (*P*=0.028) showed significant decrease but these changes were not significant in the group receiving the low-dose extract. Also, at the end of the experiment, rats were weighed again and their weights were compared. The weights in all diabetic groups (diabetic control group, the groups receiving the extract, and the group receiving glibenclamide) showed significant decrease compared to the non- diabetic control group (*P*=0.000).

Discussion

The results of this study show that the levels of glucose, LDL and cholesterol have increased in diabetic control group. Increased levels of triglycerides and serum cholesterol in STZ-diabetic rats have been reported which is in consistency with our findings. However, in Alloxan or STZ-induced diabetic rats, increased blood glucose levels indirectly increase the levels of cholesterol, TG and LDL (10) which somewhat justifies the unfavorable changes in serum lipid levels in diabetic rats in this research.

STZ was originally introduced in 1950 as an antibiotic .It is a chemical which specifically causes toxicity in pancreatic islet beta cells. In animal models, a high-dose STZ induces type-1 diabetes while a low-dose or multiple injections can cause type-2 diabetes. STZ, a glucosamine-nitrosourea compound possesses cytotoxic properties and can cause DNA damage. STZ is also used to treat metastatic islets carcinoma. In this study, the increase in blood glucose concentration in diabetic rats is due to the decrease in insulin level and its effects. The increased cholesterol level in diabetic rats is due to reduced insulin level and reduced fat storage in the liver which can lead to hyperlipidemia and high plasma cholesterol (11).

Lipids play a key role in the pathogenesis of diabetes mellitus. Serum lipids levels are usually high in diabetes mellitus which are considered as important risk factors for cardiovascular diseases. Increased concentrations of serum lipids in diabetes generally lead to increased mobilization of fatty acids from fat storage environment. Insulin inhibits the hormone-sensitive lipase (12). Therefore, the absence of insulin is considered as the main cause of the mobilization of fats from adipose tissue and increase in their plasma concentration (Table 2).

One of the ultimate goals in controlling diabetes is to reduce hyperglycemia and the associated dyslipidemia. In the present study, within 21 days, diabetes caused a significant increase in serum cholesterol and LDL compared to the non-diabetic control. The decrease in HDL was not significant that it was not consistent with the finding in the studies which examined STZ-induced diabetes over a longer period of time. It seems that a longer time frame is needed to see the effects of diabetes on HDL. Also, rats treated with glibenclamide showed a reduction in lipid profiles and an increase in HDL compared to diabetic controls which was consistent with the study done by Sharma *et al* (12) (Table 2). The results of this study showed that consumption of alcoholic extract of *S. hydrangea* had anti-hyperlipidemic effects on diabetic rats. Diabetes is characterized by the absence or deficiency of insulin leading to increased lipolysis in adipose tissue and increased free fatty acids entering the liver (1, 2).

The results indicate an increase in insulin and high-density lipoprotein (HDL) levels, as well as a reduction in cholesterol and blood glucose level in groups receiving the extract. Since most of body's energy comes from the metabolism of sugars and fats, any factor that affects the metabolism of sugars will indirectly have an adverse effect on lipid metabolism (12).

Currently available therapies for the treatment of non-insulin dependent diabetes mellitus, including dietary modification and treatment with hypoglycemic agents and insulin, have their own limitations. Studying herbal medicine, may offer a natural solution to solve the problem of diabetes in future, because they contain insulin-like substances (11). These substances bind to insulin receptors and stimulate glucose oxidation and lipogenesis in adipose tissues of young rats. The extract most probably contains substances that mimic insulin and may increase insulin secretion. Due to the effects of insulin on fat anabolism in the body tissues, especially the liver, and the reduction in blood cholesterol, it is expected that insulin-like compounds in this plant can reduce lipid concentration. Salvia species are also rich sources of polyphenolic flavonoids and phenolic acids (4). Many species of this genus as well as their isolated compounds have antioxidant properties that are significantly applied by enzymatic and non-enzymatic routes (5). Alpha- amylase is one of the key enzymes in humans responsible for the breakdown of starch into simple sugars. Inhibition of this enzyme can inhibit carbohydrate digestion and cut glucose absorption rate. It has been shown that the activity of this enzyme is also reduced by various species of Salvia including genus hydrangea (6); so this may be another way to lower blood sugar via inhibition of the enzyme.

Genus Salvia is also a rich source of terpenoids. It

has been indicated that terpenoids are useful in the treatment of diabetes (7). Flavonoids reduce abdominal fat and blood sugar, possibly by increasing the activity of proxisome receptors (13).

Inhibition of mono amino oxidase increases epinephrine and serotonin levels in body. Since epinephrine has a strong influence on the stimulation of hepatic glycogenolysis which results in the release of glucose in the blood, it can be concluded that this effect of epinephrine stimulates insulin secretion and subsequently lowers blood sugar (13).

According to the results, it is clear that the *S. hydrangea* can be used as a drug to reduce blood glucose and lipids in diabetic individuals. In addition, as the decrease in HDL in diabetes is a risk factor for cardiovascular diseases and every 0.1 mmol/lit reduction in HDL level increases the risk of heart disease by 1.5 times (14), so it may be said that using the extract can reduce the risk of heart disease; an idea that certainly requires further research.

Since flavonoids are one of the major ingredients of plant extracts, these extracts can have beneficial effects especially on diabetes. For example, glycoside isorhamnetin has inhibitory effects on aldose reductase enzyme which plays a basic role in the complications of diabetes (15). Glycoside kaempferol has hypoglycemic effects on diabetic rats and increases glucose uptake in muscles of normal Wistar rats as well (16).

Another study also reported that due to antioxidant properties, flavonoid compounds are able to neutralize free radicals and reduce their harmful effects. In patients with diabetes, free fatty acids release oxygen free radicals which result in oxidative stress. This metabolic disorder directly increases insulin resistance in the cells of the body and reduces insulin secretion (8).

Glibenclamide reduces the concentration of glucose in the blood by increasing insulin secretion from pancreatic beta cells. It seems that after prolonged use, its blood glucose lowering effects are related to out of pancreatic factors, possibly including the basal glucose production in the liver and exacerbated peripheral insulin sensitivity. The latter effect may be either due to an increase in the number of insulin receptors or the changes which happen after insulin is bound to receptors (8).

STZ selectively destroys the pancreatic insulin-secreting beta cells and causes a kind of diabetes similar to type II in humans in which reduced or no insulin production decreases glucose consumption in tissues and therefore blood glucose increases compared to non-diabetic controls (Table 1). Glibenclamide as a standard drug from sulfonylurea family is used to treat diabetes. This drug stimulates insulin secretion from beta cells. The results of the study showed that the use of ethanol extract of *S. hydrangea* at both doses significantly decreased glucose levels compared to diabetic control group. The mechanism may be related either to plasma insulin levels that were induced by the increase in insulin secretion from pancreatic beta cells or by the increase in tissue glucose consumption. However, with regard to the findings in Table 2 the former is more likely to happen (12).

The results in Table 3 indicated a significant decrease in body weight in diabetic rats compared to non-diabetic controls. As in the group receiving glibenclamide, treatment with alcoholic extract at both doses prohibited a significant weight loss compared to diabetic controls. Results showed that the effect of the extract on weight loss at both doses before and after the test was more remarkable than that of glibenclamide (12).The induction of diabetes by STZ was followed by a body weight loss in diabetic control rats which was consistent with all other similar studies .This phenomenon was because of the pathophysiology of diabetes. Compared to diabetic control group, in the group receiving glibenclamide, a statistically significant weight loss was prevented. This might be due to the stimulating activity of glibenclamide on insulin secretion from beta cells (Table 2).

On the other hand, the consumption of alcoholic extract of *S. hydrangea* at both concentrations was effective in the reduction of weight loss. This seemed to be related to insulin secretion following the consumption of the extract (Table 2). Insulin is a hormone with anabolic effects which prohibits the deterioration of protein and lipid tissues and maintains their health and growth via a metabolic change to sugar burning. In this way, it hinders weight loss (12).

In diabetic patients, the activity of adipose tissue lipoprotein lipase- the enzyme that speeds up the exchange between plasma fatty acids and fatty acids in triglycerides of adipose tissue- is reduced due to insulin deficiency which leads to reduced decomposition of lipoprotein lipids and the renal excretion of lipoproteins (17). This may cause short-term loss of body weight in diabetic rats. Since Salvia extract reduces blood lipid, there will be an increase in lipoprotein lipase activity and lipid uptake into the cells which prevents their renal excretion (18).

Conclusion

Findings of this study show that the extract of *S. hydrangea* reduces blood fat and increases insulin secretion. This effect is likely due to the flavonoids and terpenoids which are present in the extract. Finally, the extract can be suggested for the treatment of hyperlipidemia and diabetes, although a definitive conclusion can be drawn after further studies.

Several phytochemical and pharmacological studies have indicated that there are several active ingredients in *S. hydrangea* including flavonoids, tannins, phenolics and saponins which are associated with the stimulation

of beta cells of the islets which justifies their hypoglycaemic properties.

Conflict of interest

The Authors declare that they have no conflict of interest to disclose.

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References

1. Mansouri E, Khorsandi L, Abedi HA. Antioxidant effects of proanthocyanidin from grape seed on hepatic tissue injury in diabetic rats. Iran J Basic Med Sci 2014; 17:460-464.
2. Patel DK, Prasad SK, Kumar R, Hemalatha S. An overview on anti diabetic medicinal plants having insulin mimetic property. Asian Pac J Trop Biomed 2012; 2:320-330.
3. Ponnusamy S, Ravindran R, Zinjarde S, Bhargava S, Kumar AR. Evaluation of traditional Indian antidiabetic medicinal plants for human pancreatic amylase inhibitory effect *in vitro*. Evid Based Complement Alternat Med 2011; 2011:515647.
4. Nickavar B, Kamalinejad M and Izadpanah H. *In vitro* free radical scavenging activity of five Salvia species. Pak J Pharm Sci 2007; 20:291-294.
5. Perry NS, Bollen C, Perry EK and Ballard C. Salvia for dementia therapy: review of pharmacological activity and pilot tolerability clinical trial. Pharmacol Biochem Behav 2003; 75:651-659.
6. Nickavar B, Abolhasani L, Izadpanah H. α-Amylase inhibitory activities of six Salvia species Iranian. J Pharm Res 2008; 7:297-303.
7. MoridiFarimani M, Bahadori MB, Taheri S, Ebrahimi SN, Zimmermann S, *et al*. Triterpenoids with rare carbon skeletons from *Salvia hydrangea*: antiprotozoal activity and absolute configurations. J Nat Prod 2011; 74:2200-2225.
8. Zare T, Mokhtari M, Mohammadi J. The effect of hydroalcoholic extracts of *Prangos ferulacea* on blood factors of kidney and liver functions in diabetic male wistar rats. J Fasa Univ Med Sci 2012; 2:174-180.
9. Sonbolia A, Babakhanib B, Mehrabian A. Antimicrobial activity of six constituents of essential oil from Salvia. Naturforsch 2006; 61:160-164.
10. Ashraf H, Heidari R, Nejati V, Ilkhanipoo M. Preventive effect of *Berberis Integerrima* on the serum levels of glucose and lipids in streptozotocin induced diabetes in rats. J Fasa Univ Med Sci 2012; 2:148-155. (In Persian).
11. Pihlajamaki J, Gylling H, Miettinen TA, Laakso M. Insulin resistance is associated with increased cholesterol synthesis and decreased cholesterol absorption in normoglycemic men. J Lipid Res 2004; 45:507-512.
12. Sharma A, Sharma AK, Chand T, Khardiya M, Yadav KC. Antidiabetic and antihyperlipidemic activity of *Cucurbita maxima* duchense seeds on streptozotocin induced diabetic rats. J Pharmacogn Phytochem 2013; 1:108-116.
13. Nickavar B, Abolhasani L, Izadpanah H.α-Amylase inhibitory activities of six Salvia species. Iran J Pharm Res 2008; 7:297-303.
14. Asadi S, Ahmadiani A, Esmaeili MA, Sonboli A, Ansari N, Khodagholi F. *In vitro* antioxidant activities and an investigation of neuroprotection by six Salvia species from Iran: a comparative study. Food Chem Toxicol 2010; 48:1341-1349.
15. Lim SS, Jung YJ, Hyun SK, Lee YS, Choi JS. Rat lens aldose reductase inhibitory constituents of Nelumbonuciferastamens. Phytother Res 2006; 20:825-30.
16. Jorge AP, Horst H, de Sousa E, Pizzolatti MG, Silva FR. Insulino mimetic effects of Kaempferitrin on glycaemia and on 14Cglucoseuptake in rat soleus muscle. Chem Biol Interact 2004; 149:89-96.
17. Shahabinezhad M, Rahmani MR, Khaksari Hadad M, Sepehri GH, Mahmoodi M, Karimghasemi E. The effect of licorice root extract on blood sugar level in streptozotocin induced diabetic rats. J Rafsanjan Univ Med Sci 2008; 6:237-244 (In Persian).
18. Ji W, Gong BQ. Hypolipidemic activity and mechanism of purified herbal extract of *Salvia miltiorrhiza* in hyperlipidemic rats. J Ethnopharmacol 2008; 119:291–298.