Original Article

Antihyperglycemic and antihyperlipidemic effects of hydroalcoholic extract of *Securigera securidaca* seeds in streptozotocin-induced diabetic rats

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Abstract

Background: Hyperlipidemia is an associated complication of diabetes mellitus. Lowering of serum lipid levels seems to be associated with a decrease in the risk of vascular disease and related complications. The purpose of the current study was to evaluate the antihyperglycemic and antihyperlipidemic effects of the hydroalcoholic extract of *Securigera securidaca* seeds in streptozotocin-induced diabetic rats.

Materials and Methods: Female Wistar rats were randomly divided into four groups as follows: Control, diabetic, and diabetic rats treated with the *Securigera* extract at doses of 100 and 200 mg/kg. The animals were rendered diabetic by a single intraperitoneal injection of 55 mg/kg streptozotocin. Diabetic rats received the *Securigera* extract daily in drinking water from the day on which diabetes was confirmed for 4 weeks. The levels of serum glucose and lipids were spectrophotometrically measured in all groups at weeks 0 (before diabetes induction), 2, and 4.

Results: The results showed that there was a significant increase in serum glucose, triglycerides, total cholesterol, and low density lipoprotein (LDL)-cholesterol in streptozotocin-induced diabetic rats, accompanied by a decrease in high density lipoprotein (HDL)-cholesterol. Treatment of diabetic rats with *S. securidaca* seed extract at a dose of 200 mg/kg over a 4-week period significantly reduced the levels of serum glucose, total cholesterol, and LDL-cholesterol and increased the level of HDL-cholesterol, compared to diabetic untreated rats.

Conclusions: *Securigera* extract at a dose of 200 mg/kg exhibited hypoglycemic and hypolipidemic activities in streptozotocin-diabetic rats during the 4-week treatment period. This provides a valid scientific basis for using it in the treatment of diabetes in Iranian folk medicine.

Key Words: Diabetes, hyperglycemia, hyperlipidemia, rat, *Securigera securidaca*, streptozotocin

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Received: 02.10.2013, **Accepted:** 16.04.2014

Access this article online	
Quick Response Code:	Website: www.advbiores.net
	DOI: 10.4103/2277-9175.150427

INTRODUCTION

Diabetes mellitus is a chronic metabolic disease affecting about 4% of the population worldwide and its incidence is expected to increase by 5.4% in 2025.[1] Diabetes is characterized by hyperglycemia and disturbances in carbohydrate, protein, and lipid

How to cite this article: Rajaei Z, Hadjzadeh MA, Moradi R, Ghorbani A, Saghebi A. Antihyperglycemic and antihyperlipidemic effects of hydroalcoholic extract of *Securigera securidaca* seeds in streptozotocin-induced diabetic rats. Adv Biomed Res 2015;4:33.

metabolism. Chronic hyperglycemia that occurs in diabetes is associated with long-term damage, dysfunction, and failure of different organs, especially the eyes, kidneys, nerves, heart, and blood vessels.[2] Diabetes is also associated with profound alterations in the plasma lipid and lipoprotein profile and an increased risk of premature atherosclerosis, coronary insufficiency, and myocardial infarction.[3]

Despite the notable progress shown in the management of diabetes mellitus by synthetic drugs, there has been a growing interest in medicinal plants for their therapeutic properties. Herbal remedies are apparently effective, produce minimal or no side effects in clinical experience, and are of relatively low cost, as compared to oral synthetic hypoglycemic agents.[4-6]

Securigera securidaca (Fabaceae), locally known as "Gandeh Talkheh" in Persian, is an annual herb distributed in West Asia, Europe, and Africa. Phytochemical analysis of the ethanolic and aqueous extracts of *S. securidaca* seed has revealed the presence of flavonoids, steroidal and pentacyclic triterpenoid-type saponins, cardenolides, and tannins.[7,8]

The seeds of the plant are used in Iranian folk medicine to treat several ailments such as hypertension, hyperlipidemia, and diabetes.[9] It has been shown that the extracts from the seeds of *S. securidaca* have different activities such as antiepileptic,[10] marked chronotropic, diuretic, hypokalemic,[11] and antiulcerogenic activities.[12] Till date, only limited experimental studies are available showing the antihyperglycemic and/or hypolipidemic activity of *S. securidaca*. The hypoglycemic effect of *S. securidaca* seeds has been reported in alloxan-induced diabetes.[8,13] Recently, the effect of *S. securidaca* seeds in lowering serum low density lipoprotein (LDL)-cholesterol and triglyceride levels was found in hypercholesterolemic rats by Garjani *et al*.[14] However, none of the studies have reported on the hypolipidemic activity of *S. securidaca* seeds in experimental diabetes. In this study, we investigated the antihyperglycemic and hypolipidemic effects of hydroalcoholic extract of *S. securidaca* seeds in a streptozotocin-induced diabetic model.

MATERIALS AND METHODS

Preparation of the hydroalcoholic extract

S. securidaca seeds were purchased from Imam Reza Pharmacy and graciously identified by Ferdowsi University herbarium, Mashhad, Iran (Herbarium Accession No. 160-1901-11). The powdered seeds (860 g) were macerated in 3200 ml of 70% ethanol/H_2O for 72 h. Then the hydroalcoholic extract was filtered and concentrated in an oven at 40-45°C for 72 h. The resulting extract on drying gave 102.6 g (i.e. 11.86% yield) of brownish extract. The plant extract was dissolved in water for pharmacological experiments.

Animals

Female Wistar rats weighing 200-230g were housed in an air-conditioned colony room at 23 ± 2°C on a standard pellet diet and tap water *ad libitum*. The experiments were conducted in accordance with the Guide for the Care and Use of Laboratory Animals, and the study was approved by Mashhad University of Medical Sciences.

Induction of diabetes

The overnight fasted rats were rendered diabetic by a single intraperitoneal injection of 55 mg/kg streptozotocin (Enzo Life Sciences, New York, USA)[5] freshly dissolved in cold distilled water. After 72 h of administering streptozotocin injection, serum glucose levels were measured using a glucometer (Glucocard, Kyoto, Japan). Only those animals with serum glucose higher than 250 mg/dl were selected as diabetics for the following experiments. The day on which hyperglycemia had been confirmed was designated as day 0. Diabetes was also confirmed by the presence of polyphagia, polydipsia, and polyuria during the experiment.

Experimental design

Rats were randomly allocated to four groups as follows: Control (n = 8), diabetic (n = 8), diabetics treated with the extract of *Securigera* in drinking water at doses of 100 mg/kg (*Securigera* 100 mg/kg, n = 10) and 200 mg/kg (*Securigera* 200 mg/kg, n = 10). The animals received the *Securigera* extracts in drinking water from day 0 for 4 weeks. Changes in body weight, food consumption, and water intake were regularly recorded during the experimental period. For blood sampling, the rats were fasted overnight and blood samples were obtained from retro-orbital plexus before diabetes induction (week 0) and at the end of weeks 2 and 4. Blood was allowed to clot and the serum separated by centrifugation at 3500 × g for 10 min.

Biochemical parameters

Serum concentrations of glucose, triglycerides (TG), total cholesterol (TC), and high density lipoprotein (HDL)-cholesterol were determined by enzymatic colorimetric methods using commercially available kits (Pars Azmun, Tehran, Iran) by a biochemistry analyzer (Convergys 100, Germany). The assay was performed according to the manufacturer's instructions. Very low density

lipoprotein (VLDL)-cholesterol was calculated as TG/5, and LDL-cholesterol was estimated by using Friedewald formula[15] as follows:

LDL (mg/dl) = TC − (HDL + VLDL)

Statistical analysis

The data were expressed as mean ± SEM. Statistical analysis was carried out using one-way analysis of variance (ANOVA) followed by Tukey's *post-hoc* test. A statistical P value less than 0.05 was considered significant.

RESULTS

Effects of *Securigera* extract on serum glucose levels

Measurement of serum glucose levels indicated that before diabetes induction (week 0), there were no significant differences among animals in the experimental groups [Figure 1]. Diabetic rats showed a significant increase in serum glucose levels compared to control rats at weeks 2 and 4 ($P < 0.001$) [Figure 1]. Treatment of diabetic rats for 2 weeks with *Securigera* extract at doses of 100 and 200 mg/kg did not change the serum glucose levels in comparison to untreated diabetic rats. At week 4, treatment of diabetic rats with *Securigera* extract at a dose of 100 mg/kg had no effect on the serum glucose levels. However, treatment with *Securigera* extract at a dose of 200 mg/kg significantly decreased the serum glucose levels compared to diabetic rats ($P < 0.001$) [Figure 1].

Effects of *Securigera* extract on serum lipid profile

Regarding serum lipids, one-way ANOVA revealed that diabetes induction for 4 weeks caused a significant increase in TG levels compared to baseline data ($P < 0.05$) [Figure 2] and treatment of diabetic rats with *Securigera* extract had no effect on TG levels.

Meanwhile, the levels of TC and LDL-cholesterol were significantly increased ($P < 0.001$) [Figures 3 and 4] and the levels of HDL-cholesterol were significantly decreased ($P < 0.01$) [Figure 5] in diabetic rats compared to control rats at week 4. Treatment of diabetic rats with *Securigera* extract at a dose of 200 mg/kg for 4 weeks significantly reduced the levels of TC and LDL-cholesterol ($P < 0.05$ and $P < 0.01$, respectively) [Figures 3 and 4] and significantly increased HDL-cholesterol levels compared to diabetic animals ($P < 0.05$) [Figure 5].

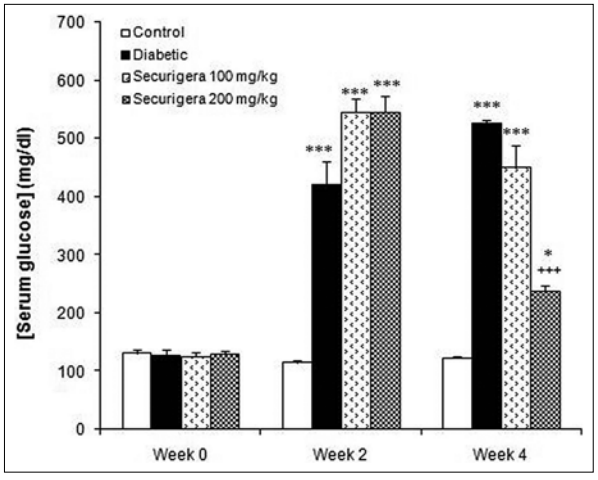

Figure 1: Serum glucose levels in the control (n=8), diabetic (n=8) and diabetic rats treated with the Securigera extract at doses of 100 (n=10) and 200 mg/kg (n=10) at week 0 (before diabetes induction) and at the end of weeks 2 and 4. Data are mean ± SEM. *P<0.05, ***P<0.001 vs control group, ^{+++}P<0.001 vs diabetic group

DISCUSSION

This study was carried out in order to find the influence of daily oral administration of the hydroalcoholic extract of *S. securidaca* seeds for 4 weeks on plasma glucose and lipid profile in diabetic rats. In our study, streptozotocin was selected for induction of diabetes in rats. Treatment of rats with streptozotocin is an established model for inducing type 1 or insulin-dependent diabetes. In the present study, streptozotocin-induced diabetic rats showed significant increase in plasma glucose levels when compared to normal rats. The increased levels of plasma glucose were decreased upon treatment with hydroalcoholic extract of *S. securidaca* seeds at a dose of 200 mg/kg. Our findings are in accordance with the results of other authors who have reported the antihyperglycemic effects of *S. securidaca* extract in diabetic animals.[8,11,13] Contrary to this, Minaiyan *et al*. have reported that oral administration of the hydroalcoholic extract of *S. securidaca* at doses of 200, 400, and 800 mg/kg and intraperitoneal administration at a dose of 400 mg/kg to streptozotocin-induced diabetic rats were not able to reduce the blood glucose levels at 1, 2, 3, 4, and 8 h after treatment.[16] This discrepancy could be in part due to the acute administration of the extract and dosage of the extract. According to our results, it seems that chronic treatment with *Securigera* extract at lower doses is more effective in reducing the blood glucose levels in streptozotocin diabetic rats.

The hypoglycemic action of *S. securidaca* extract may either be due to enhanced insulin secretion from remnant pancreatic β-cells or protection of intact functional β-cells from further deterioration so that they remain active and continue to produce insulin, as observed by the significant increase in the level of insulin in diabetic treated rats. Pouramir *et al*. recently

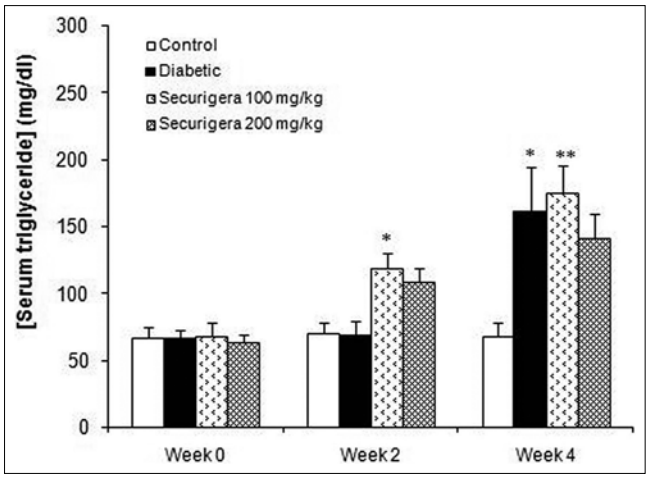

Figure 2: Serum TG levels in the control (n = 8), diabetic (n = 8), and diabetic rats treated with the *Securigera* extract at doses of 100 (n = 10) and 200 mg/kg (n = 10) at week 0 (before diabetes induction) and at the end of weeks 2 and 4. Data are mean ± SEM. *P < 0.05, **P < 0.01 vs. control group

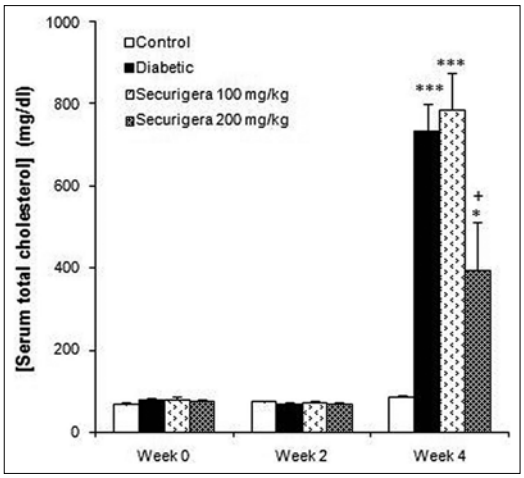

Figure 3: Serum TC levels in the control (n = 8), diabetic (n = 8), and diabetic rats treated with the *Securigera* extract at doses of 100 (n = 10) and 200 mg/kg (n = 10) at week 0 (before diabetes induction) and at the end of weeks 2 and 4. Data are mean ± SEM. *P < 0.05, ***P < 0.001 vs. control group, ^{+}P < 0.05 vs. diabetic group

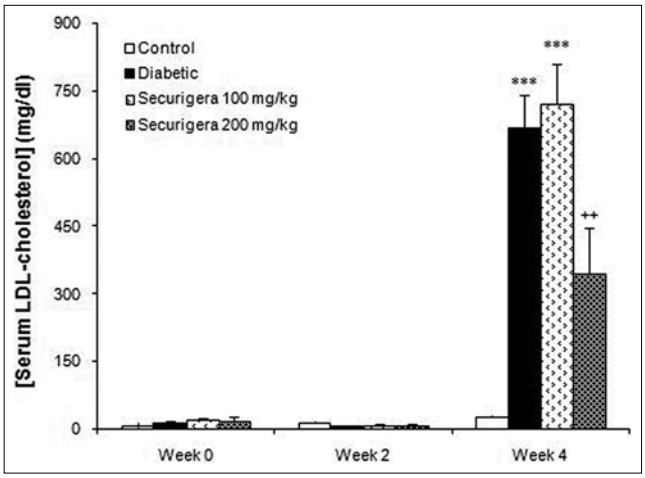

Figure 4: Serum LDL-cholesterol levels in the control (n = 8), diabetic (n = 8), and diabetic rats treated with the *Securigera* extract at doses of 100 (n = 10) and 200 mg/kg (n = 10) at week 0 (before diabetes induction) and at the end of weeks 2 and 4. Data are mean ± SEM. ***P < 0.001 vs. control group, ^{+}P < 0.01 vs. diabetic group

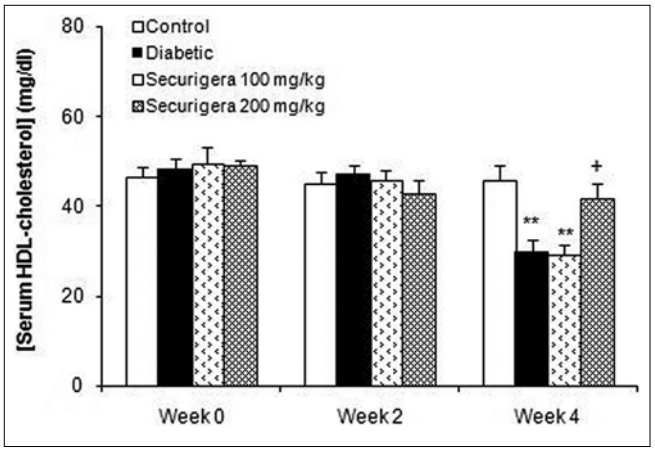

Figure 5: Serum HDL-cholesterol levels in the control (n = 8), diabetic (n = 8), and diabetic rats treated with the *Securigera* extract at doses of 100 (n = 10) and 200 mg/kg (n = 10) at week 0 (before diabetes induction) and at the end of weeks 2 and 4. Data are mean ± SEM. **P < 0.01 vs. control group, ^{+}P < 0.05 vs. diabetic group

reported that treatment with the extract of *S. securidaca* seeds reduced the blood glucose levels by increasing the insulin levels in alloxan-induced diabetic rats.[13]

Hyperlipidemia is also a known complication of diabetes mellitus[17] and is characterized by increased levels of cholesterol, TG, and phospholipids and also changes in lipoproteins.[18] Hypercholesterolemia and hypertriglyceridemia in streptozotocin-induced diabetic rats are also well documented.[19] The high level of TC in blood could be considered as a major risk factor causing coronary heart disease.[20]

In our experiment, significantly increased levels of plasma TC, TG, and LDL-cholesterol and decreased levels of HDL-cholesterol were observed in streptozotocin-diabetic rats. Increased mobilization of free fatty acids from the peripheral fat depots leads to abnormally high concentration of serum lipids in diabetes, since insulin inhibits hormone-sensitive lipase. During diabetes, enhanced activity of this enzyme increases lipolysis and releases more free fatty acids into the circulation.[21] Excess production of serum fatty acids promotes the conversion of excess fatty acids into phospholipids and cholesterol in the liver. These two substances along with excess of TG formed in the liver may be discharged into the blood in the form of lipoproteins.[22]

High levels of TC and, most importantly, LDL-cholesterol are the predictors of atherosclerosis.[23] Lowering of

serum lipid levels through dietary or drug therapy seems to be associated with a decrease in the risk of vascular disease and related complications.[24] In the present study, treatment with the hydroalcoholic extract of *S. securidaca* seeds at a dose of 200 mg/kg markedly decreased both serum TC and LDL-cholesterol levels in diabetic animals. There was also an increase in HDL-cholesterol levels, which plays an important role in the treatment of hypercholesterolemia, since several studies have shown that an increase in HDL-cholesterol is associated with a decrease in coronary risk.[25] To our knowledge, this is the first study reporting the hypolipidemic activity of *S. securidaca* seed extract in streptozotocin-induced diabetes. Previously, Garjani *et al*. had reported the effect of *S. securidaca* seeds in lowering serum LDL-cholesterol and TG levels in hypercholesterolemic rats.[14]

The underlying mechanism by which *Securigera* extract exerts its cholesterol-lowering effect seems to be by causing a decrease in cholesterol absorption from the intestine by binding with bile acids within the intestine and increasing the excretion of bile acids.[26,27] *Securigera* extract can also act by decreasing the cholesterol biosynthesis, especially by decreasing the activity of 3-hydroxy-3-methyl-glutaryl coenzyme A reductase (HMG-CoA reductase), a key enzyme of cholesterol biosynthesis.[28,29] In addition, *Securigera* seeds may treat hypercholesterolemia via enhanced uptake of LDL by increasing the LDL receptors.[30]

The phytochemical analysis of ethanolic and aqueous extracts of *S. securidaca* seeds has revealed the presence of flavonoids, steroidal and pentacyclic triterpenoid-type saponins, cardenolides, and tannins.[7,8] One or more of these chemical compounds of the plant are also likely to have contributed to the observed hypolipidemic activity of the hydroalcoholic extract of *S. securidaca* seeds. Flavonoids function as powerful antioxidants and some are reported to have anti-diabetic activity.[31] Bhavna *et al*. reported that flavonoid-rich extract from the seeds of *Eugenia jambolana* possesses significant hypoglycemic and hypolipidemic activities in streptozotocin-induced diabetic rats.[32] Furthermore, it has been shown that saponins isolated from different plants produce significant hypolipidemic effects mainly by suppression of cholesterol luminal absorption and also by increase of cholesterol secretion through biliary excretion.[33,34] Therefore, the hypolipidemic activity of *Securigera* extract can be attributed to the presence of flavonoids and saponins.

In conclusion, the hydroalcoholic extract of *S. securidaca* seeds showed hypoglycemic and hypolipidemic activities in streptozotocin diabetic rats during the 4-week treatment period and this confirms its use in Iranian phytomedicine. Further studies are needed to determine the constituents of the extract and the mechanism (s) by which *Securigera* extract exerts its anti-diabetic effects.

ACKNOWLEDGMENTS

The results presented in this work have been taken from a student's thesis. This study was supported by the Council of Research, Mashhad University of Medical Sciences.

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Source of Support: Council of Research, Mashhad University of Medical Sciences. **Conflict of Interest:** None declared.