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Research Article

Effect of *Solanum nigrum* L. on blood glucose concentration and lipid profile in normal and STZ-induced diabetic rats

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ABSTRACT: **Background:** Fruits of *Solanum nigrum* L. (Solanaceae) are used in traditional medicine for a number of ailments including metabolic disorders. **Objectives:** The ethanolic extract of fruits of *Solanum nigrum* L. (SNE) was investigated to evaluate the effects of on blood glucose concentration, lipid profile and renal function tests and their possible mechanism of action involved in these activities. **Materials and Methods:** SNE (100 and 250 mg/kg; p.o.) was administered to diabetic rats and the standard drug Insulin (5 I.U. /kg; i.p.) to a group serving as positive control. Effects of SNE on various biochemical parameters were studied in diabetic rats. **Results:** Oral administration of SNE (100 and 250 mg/kg.) for 21 days to streptozotocin-induced diabetes rats significantly ($p<0.05$) decreased the levels of blood glucose and improved the levels of plasma insulin. The levels of triglycerides, cholesterol, high density lipoprotein (HDL), low density lipoprotein (LDL), very low density lipoprotein (VLDL), aspartate amino transferase (AST) and alanine amino transferase (ALT), urea and creatinine, were markedly altered in STZ-induced diabetic rats. Oral administration of SNE restored all these biochemical parameters to near control levels.
Discussion and Conclusions: The present study reveals the efficacy of *Solanum nigrum* fruit extract in the amelioration of diabetes and its associated complications. The anti-diabetic and anti-hyperlipidemic effect of *Solanum nigrum* was also compared with insulin, a standard drug.

KEYWORDS: *Solanum nigrum*, diabetes mellitus, blood glucose, lipidprofile, nephroprotection, streptozotocin

INTRODUCTION

Diabetes mellitus is a disorder of carbohydrate, fat and protein metabolism attributed to diminished production of insulin or mounting resistance to its action. Chronic hyperglycemia during diabetes causes glycation of body proteins that in turn leads to secondary complications affecting eyes, kidneys, nerves and arteries.[1] These affects may be delayed, lessened or prevented by maintaining blood glucose values close to normal. To date, there are different groups of oral hypoglycemic agents for clinical use, having characteristic profiles of side effects.[2,3] Despite the fact that appreciable progress has been made in the management of diabetes mellitus using conventional anti-diabetic management strategies, the search for plant-based products for the control of diabetes mellitus continues with great expectation. Traditional medicines derived mainly from plants play a major role in the management of diabetes mellitus.[4] World Health Organization (WHO) has recommended the evaluation of traditional plant treatments for diabetes as they are effective, non-toxic, with less or no side effects and are considered to be excellent candidates for oral therapy.[5] The present work was undertaken to explore the antidiabetic potential of the plant *Solanum nigrum* in type 1 diabetic animals.

Solanum nigrum Linn. (Solanaceae), commonly known as 'Black nightshade', has been extensively used in traditional medicine in India and other parts of world to cure liver disorders, chronic skin ailments (psoriasis and ringworm), inflammatory conditions, painful periods, fevers, diarrhoea, eye diseases, hydrophobia, etc.[6,7] Our research interest in this plant arose because of its potential medicinal value against diabetes, as used in folk medicine.[8]

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It has an erect, angular, branching stem and grows 1 to 2 feet in height and may be glabrous or covered with inward- bent hairs. The leaves are alternate, dark green, ovate, and wavy toothed or nearly entire. The fruit is a many-seeded, pea sized, purple or black berry. It grows as a weed all over dry parts of India. The plant contains glycoalkaloids (solanine, solamargine, solanigrine and solasodine), steroidal glycosides (β-solamargine, solasonine and α, β-solansodamine), steroidal saponins (diosgenin), steroidal genin (gitogenin), tannin and polyphenolic compounds.[9,10] *Solanum nigrum* fruits are very commonly used as hepatoprotective agents,[11] which also afford protection against free radical mediated damage.[12] The plant also exerts cytoprotection against gentamycin-induced toxicity on vero cells.[13] In the previous study, we demonstrated a glucose lowering effect of ethanolic fruit extract in fructose induced hyperglycemia and hyperlipidemia.[14] The main objective of the present work was to evaluate the antidiabetic, hypolipidemic and nephroprotective potential of an ethanolic extract of *Solanum nigrum* (SNE). SNE was administered orally over a period of 21 days, and the effect of *Solanum nigrum* was compared with insulin as a reference hypoglycemic drug.

MATERIALS AND METHODS

Chemicals

Streptozotocin (STZ) used for the induction of diabetes was procured from Sisco Research Laboratory Pvt. Ltd., India. Insulin was procured from a local market (Human Mixtard, Novo Nordisk India Pvt. Ltd.). All other reagents used in the experiment were of analytical grade.

Preparation of extract

Fresh fruits of *Solanum nigrum* were collected in October 2007 from the region of Anand, Gujarat. The plant was authenticated by comparison with voucher specimen No. VSM 502 and ARM 2174 at the Prof. G.L.Shah Herbarium of S.P.University, Vallabh Vidyanagar, Anand, Gujarat, India. An extract was prepared by soxhlet extraction of the crushed fresh fruits with ethanol. The extract was filtered and then evaporated to dryness (7.9% w/w yield). The extract was stored in desiccators for use in subsequent experiments.

Determination of total phenolic content

Total phenolic content of SNE extract were determined by the Folin–Ciocalteu procedure by using gallic acid as a standard phenolic compound.[15] 1 ml of extract solution (1000 µg/ml) in a volumetric flask was diluted with distilled water (46 ml). Folin–Ciocalteu reagent (1 ml) was added and the contents of the flask were mixed thoroughly. After 3 min, 3 ml of Na_2CO_3 (2%) was added, then the mixture was allowed to stand for 2 h with intermittent shaking. The absorbance was measured at 760 nm in a spectrophotometer (Shimadzu Pharma Spec UV – 1700, Japan). The amount of total phenolic compounds in the SNE extracts was determined in micrograms of gallic acid equivalent, using the equation obtained from the standard gallic acid graph:

$$\text{Absorbance} = 0.0048 \times \text{Total phenols [Gallic acid equivalents (µg)]} - 0.0931$$

Animals

Wistar albino rats (200–250 g) housed under well controlled conditions of temperature (22 ± 2°C), humidity (55 ± 5%) and 12/12-h light/dark cycles, were given access to food and water ad libitum. The protocol of the experiment was approved by the Institutional Animal Ethical Committee as per the guidance of the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA), Ministry of Social Justice and Empowerment, Government of India.

Acute toxicity study

Healthy adult Wistar rats of either sex fasted overnight but allowed access to water ad libitum, were randomly divided into five groups (n = 5, either sex). The first group (control group) received water. Groups 2–5 were orally treated with the ethanolic extract of *Solanum nigrum* at the doses of 0.5, 1.0, 1.5, 2.0 and 2.5 g/kg, respectively. Animals were observed for hazardous symptoms and mortality for a period of 3 days after treatment. The results indicated that acute treatment of *Solanum nigrum* extract by oral route at dose of 2.5 g/kg did not produce any sign of toxicity or death in rats during the 14 days of observation. Therefore, the LD_{50} could not be estimated, and it is presumably more than 2.5 g/kg.

Effect of *S. nigrum* ethanol extract in normal rats

Eighteen healthy adult Wistar rats of either sex were divided into three groups of six animals each for the normoglycemic study. Test groups were treated with SNE at 100 and 250 mg/kg, respectively by oral route once a day for twenty one days, whilst the control group received only vehicle (0.25% NaCMC). After overnight fasting, blood samples were withdrawn from retro orbital plexus of each animal for biochemical estimation on day 21.

Induction of diabetes

Hyperglycemia was induced in overnight fasted adult Wistar strain albino rats weighing 200–250 g by a single intraperitoneal injection of 50 mg/kg streptozotocin (dissolved in 0.1 M ice-cold citrate buffer, pH

4.5, immediately before use) in a volume 1ml/kg body weight[16] followed by glucose solution (5%) supplementation in drinking water for 72 h to avoid hypoglycemia. Non-diabetic control animals received a citrate buffer injection. Hyperglycemia was confirmed by measuring blood glucose, determined at 48 h after injection.[17] Only rats with fasting blood glucose levels greater than 200 mg/dL were considered diabetic and then included in this study. The rats found hyperglycemic were screened for the anti hyperglycemic study.

Experimental design

The experimental animals were then divided into the following four groups, (1) Normal Control, (2) Diabetic control, (3) Diabetic control treated with SNE (100 mg/kg body weight, p.o.) (4) Diabetic control treated with SNE (250 mg/kg body weight, p.o.) and (5) Diabetic control treated with insulin (5 I.U/kg, s.c.). Treatment was given daily for 21 days. The control group received an equal volume of the vehicle. During the study, standard food and water were provided ad libitum. All treatments started 72 hours after streptozotocin injection. At the end of 21 days, rats were fasted overnight and blood samples were collected for estimation of biochemical parameters.

Oral glucose tolerance test (OGTT)

The OGTT was performed in overnight fasted normal control, normal control treated with SNE (100 and 250 mg/kg), diabetic control, diabetic control treated with SNE (100 and 250 mg/kg) and diabetic control treated with insulin groups, at the end of the 21-day treatment. All animals received a load of 2.5 g of glucose/kg (p.o). Blood glucose was measured in blood withdrawn from the retro orbital plexus, before load (t = 0) and 30, 60, and 120 min after glucose administration. Blood glucose level was measured with the help of one touch glucometer (Life Scan, Inc., Johnson & Johnson Company, USA). The results were expressed as integrated area under the curve (AUC) for glucose and insulin, that was calculated by the trapezoid rule [AUC= (C1 +/C2)/2 × ($t_1 - t_2$)] and changes in glucose concentrations during OGTT were expressed as AUCglucose (mg/dl per min).

Biochemical estimation

Blood glucose level was estimated by the one touch glucometer. Serum was separated from the blood samples and was used for the biochemical analysis. Serum insulin was determined by radioimmunoassay (RIA) using a commercial rat insulin kit. Serum cholesterol, serum triglycerides and serum high-density lipoprotein (HDL) cholesterol, serum creatinine and serum urea were determined using diagnostic reagent kits (Kruise pathline Pvt. Ltd, India). In addition to the above parameters, VLDL-cholesterol and LDL-cholesterol were calculated as per equations below.[18]

VLDL = Serum triglyceride/5

LDL = Total serum Cholesterol – [Total serum triglycerides/5] – Total serum HDL-C

Statistical analysis

Data were statistically calculated by utilizing one way ANOVA and expressed as mean ± S.E.M. followed by Dunnett's t-test using computerized GraphPad InStat version 3.05, Graph pad software, USA.

RESULTS

Determination of total phenolic content

Quantitative analysis showed that SNE contained 50.645 mg/g gallic acid equivalents of phenolic compounds.

Acute toxicity study

The SNE was found to be safe up to 2500 mg/kg with no sign of mortality or change in behavioral pattern. This result suggests that the plant extract is found to be not toxic and safe to use at the 2500 mg/kg dosage.

Effect of *S. nigrum* ethanol extract in normal rats

Two doses of SNE (100 and 250 mg/kg) were evaluated in fasted normal rats. Table 1 depicts the effects of SNE given by oral route at doses 100 and 250 mg/kg for 21 days on different biochemical parameters. Treatment with SNE at all the doses prevented increase in $AUC_{glucose}$ at significant ($p<0.05$) extent as compared to normal control animals. The extract (100, 250 mg/kg) did not produce any significant effect on the serum glucose, lipid profile and renal function tests in normal Wistar rats. Our study reveals that SNE does not produce any toxicity and could be safely used for therapeutic purpose at the doses studied.

Effect of *S. nigrum* ethanol extract in diabetic rats

The effect of ethanol extract of matured fruits of *Solanum nigrum* on streptozotocin induced diabetic animals ispresented in Table 2. STZ induced diabetic rats (diabetic control) exhibited significant hyperglycemia with a corresponding hypoinsulinemia as compared to normal control rats. Treatment with SNE (100 and 250 mg/kg) or insulin produced a significant ($p < 0.05$) decrease in the elevated serum glucose levels and serum insulin levels compared to the diabetic control group.

During OGTT when further glucose load was given to the STZ-induced type 1 diabetic rats, there was further rise in glucose levels observed at 0, 30, 60 and 120 min

Table 1: Effect of ethanolic extract of *Solanum nigrum* (SNE) on various parameters in normal rats

Parameters	Normal control	Normal control treated with SNE (100 mg/kg)	Normal control treated with SNE (250 mg/kg)
Blood glucose (mg/dl)	96.63 ± 6.47	91.49 ± 6.86	89.13 ± 6.25
$AUC_{glucose}$ (mg/dl.min)×10^3	4.11 ± 0.09	3.38 ± 0.17*	3.15 ± 0.13*
Serum insulin (µU/ml)	5.55 ± 0.55	5.34 ± 0.56	5.27 ± 0.58
Serum cholesterol (mg/dl)	111.83 ± 6.10	112.19 ± 6.07	107.36 ± 6.27
Serum triglyceride	86.07 ± 5.49	88.59 ± 4.87	82.33 ± 5.78
HDL-cholesterol	37.58 ± 2.05	38.28 ± 2.18	39.03 ± 2.01
LDL-cholesterol	57.03 ± 3.37	56.19 ± 4.10	51.86 ± 3.70
VLDL-cholesterol	17.21 ± 1.10	17.71 ± 0.97	16.46 ± 1.15
Serum creatinine	0.78 ± 0.05	0.86 ± 0.11	0.91 ± 0.09
Serum urea	29.85 ± 2.18	27.88 ± 2.53	31.45 ± 2.27

Values are expressed as mean ± S.E.M. (n = 6). *P < 0.05, when compared with normal control.

Table 2: Effect of ethanolic extract of *Solanum nigrum* (SNE) on various parameters in diabetic rats

Parameters	Normal control	Diabetic control	Diabetic control treated with SNE (100 mg/kg)	Diabetic control treated with SNE (250 mg/kg)	Diabetic control treated with insulin (5 I.U./kg)
Blood glucose (mg/dl)	96.63 ± 6.47	388.36 ± 19.46 *	235.11 ± 17.46**	191.99 ± 18.41**	158.35 ± 5.57**
$AUC_{glucose}$ (mg/dl.min)×10^3	4.11 ± 0.09	13.21 ± 0.10*	9.85 ± 0.43**	8.97 ± 0.49**	8.84 ± 0.61**
Serum insulin (µU/ml)	5.55 ± 0.55	1.96 ± 0.29*	3.01 ± 0.28**	3.86 ± 0.23**	5.69 ± 0.56**
Serum cholesterol (mg/dl)	111.83 ± 6.10	167.49 ± 5.04*	141.10 ± 7.52**	126.44 ± 6.95**	88.69 ± 4.80**
Serum triglyceride	86.07 ± 5.49	167.97 ± 8.05*	136.81 ± 7.57**	107.31 ± 5.58**	127.15 ± 5.39**
HDL-cholesterol	37.58 ± 2.05	28.00 ± 2.21*	39.25 ± 2.79**	36.58 ± 2.57**	33.27 ± 1.94**
LDL-cholesterol	57.03 ± 3.37	105.88 ± 5.13*	74.49 ± 9.66**	68.40 ± 7.08**	29.98 ± 5.90**
VLDL-cholesterol	17.21 ± 1.10	33.59 ± 1.61*	27.36 ± 1.51**	21.46 ± 1.11**	25.43 ± 1.08**
Serum creatinine	0.78 ± 0.057	1.80 ± 0.10*	1.22 ± 0.11**	1.13 ± 0.084**	1.43 ± 0.056**
Serum urea	29.85 ± 2.18	49.07 ± 2.94*	31.56 ± 2.95**	26.05 ± 1.70**	33.00 ± 2.63**

Values are expressed as mean ± S.E.M. (n = 6). *P < 0.05, when compared with normal control. **P < 0.05, when compared with diabetic control.

as compared to non diabetic control rats (data was not shown). Results of oral glucose tolerance test revealed that $AUC_{glucose}$ significantly ($p<0.05$) increased in diabetic control as compared to non-diabetic control. Treatment with SNE significantly ($p<0.05$) decreased elevated $AUC_{glucose}$ of diabetic animals. Serum triglyceride, total cholesterol, LDL-cholesterol and VLDL-cholesterol levels were found to be increased significant ($p<0.05$) in STZ induced diabetic rats as compared to non diabetic control. HDL-cholesterol was found to be significantly ($p<0.05$) decreased in diabetic rats. Treatment with SNE (100 and 250 mg/kg) produced a significant reduction in elevated serum triglyceride, total cholesterol, LDL-cholesterol and VLDL-cholesterol levels in diabetic rats and a significant improvement in HDL-cholesterol levels in diabetic rats. STZ-induced type 1 diabetic rats showed a significant ($p < 0.05$) increase in serum creatinine and urea levels as compared to non diabetic control rats. Treatment with SNE (100 and 250 mg/kg, p.o.) produced significant decrease in serum creatinine and urea levels in diabetic rats.

DISCUSSION

The fruit of *Solanum nigrum* is well known for its medicinal properties in the ayurvedic system of medicine. Some of these medicinal properties have been demonstrated in experimental studies carried out on the alcoholic extract of *Solanum nigrum*. Within the context of present investigation, we evaluated the effect of SNE on various biochemical parameters in STZ induced diabetic rats.

Streptozotocin, an N-nitroso derivative of glucosamine[22] is a potent toxin for β cell of islet of Langerhans of pancreas and causes hyperglycemia, hyperlipidemia and renal damage in rats.[23–25] This study focused on exploring the effectiveness of SNE for the correction of diabetes and its associated complications, to prove the folklore claims. The present work has detected the anti-diabetic, lipid lowering and thus the nephroprotective effects of SNE in STZ-induced type I diabetic rats.

Although herbal drugs are generally considered to be safe, there are reports on the toxicity of several of these preparations.[19–21] In view of such reports and to ascertain the safe use of crude SNE, the present study was carried out to evaluate its effect on various biochemical parameters. Treatment of normal rats with SNE at doses of 100 and 250 mg/kg for a period of 21 days did not produce a significant change in the levels of serum glucose, lipid profile and renal function tests. Our study did not show any change in the levels of biochemical parameters suggesting thereby that the body homeostasis was not disturbed by SNE administration. However, SNE treatment at the dose of 100 and 250 mg/kg showed significant decrease in $AUC_{glucose}$ on orally administered glucose load in oral glucose tolerance test in normal rats. These increased glucose disappearance rates may be due to increase insulin release that would be expected with increased glucose administration. In our investigation, the results of the oral glucose tolerance test revealed that the alcoholic extract of the fruit has the capacity to lower blood glucose levels in normal rats.

Our present findings showed that the total phenolic content of SNE was 50.645 ± 3.40 mg/g. Several classes of chemicals have been found in SNE including flavonoids and phenolic compounds.[10] Several phenolic compounds possess marked anti-diabetic activity.[26]

The results of the present investigation indicate that SNE reduces the glucose level and improve insulin levels in diabetic rats and improves glucose tolerance in diabetic animals. OGTT data over 2 h indicates that SNE reduced plasma glucose concentration in STZ-diabetic rats. These effects may be attributed to either an increase in insulin secretion or an inhibition of intestinal absorption of glucose and an increase in glucose metabolism. Since STZ selectively destroys β-cells of the pancreas, we would expect the extract to exert an effect on blood glucose concentrations in STZ-diabetic rats through insulin production by the remaining β-cells of pancreas. Therefore, the present results suggest that the antihyperglycemic effect observed with SNE may appear to involve mechanisms that involve insulin secretion. This is supported by the increase in serum insulin levels following SNE treatment seen in these studies.

Several workers have shown that hyperglycemia and hyperlipidemia are the common characteristics of STZ-induced diabetes mellitus in experimental animals.[27–29] and presents a serious risk of vascular disease. In the present investigation, the STZ induced diabetic rats were found to produce increased levels of serum in triglycerides, total cholesterol, LDL cholesterol and VLDL cholesterol levels. This correlates with earlier studies which report that there is an increase in lipid levels is observed not only in diabetic animals but also in diabetic patients.[30] Chronic treatment of SNE produced a significant decrease in hypercholesterolemia and hypertriglyceridemia in diabetic rats. Thus, apart from the regulation of carbohydrate metabolism, SNE also played an important role in the metabolism of lipids. The possible mechanism for decreased lipid levels could be either insulin releasing effect of SNE or insulin sensitizing activity, because insulin has been proved to inhibit the activity of the hormone sensitive lipase in adipose tissue and suppresses the release of lipids.[31] The HDL-cholesterol is involved in transport of cholesterol from peripheral tissues to liver and thereby acts as protective factor. In the present study, level of HDL-cholesterol was found to be decreased in diabetic rats. The level of HDL-cholesterol was increased in STZ induced diabetic rats when treated with SNE. This indicates that SNE may have the additional benefit of helping to increase transport of peripheral tissue cholesterol to liver, thereby decreasing blood cholesterol levels.

STZ diabetic animals showed a significant elevation of serum creatinine and urea levels as compared to non diabetic control animals, indicating impaired renal function of diabetic animals which is consistent with the earlier findings.[32,33] The increase in serum creatinine and urea levels may result from hyperglycemia causing osmotic diuresis and depletion of extracellular fluids. Treatment with SNE was found to decrease serum creatinine and urea levels. This may be correlated with a decrease in glucose levels induced by SNE.

On the basis of these results, it could be concluded that the use of *Solanum nigrum* in folk medicine has a high correlation with scientific data observed in this study, where the extract has shown significant antihyperglycemic and antihyperlipidemic as well as nephroprotective potentials in experimental animals.

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CONFLICT OF INTEREST

The Author(s) declare(s) that they have no conflicts of interest to disclose.

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