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Research Article

ANTIDIABETIC EFFECTS OF [10]-GINGEROL IN STREPTOZOTOCIN- AND HIGH-FAT DIET-INDUCED DIABETIC RATS

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ABSTRACT

Objective: India is the "diabetes capital of the world" with 62.4 million Indians having type 2 diabetes in 2011. A major risk factor for insulin resistance is obesity, which is generally caused by regular physical inactivity and high-fat diet (HFD). Obesity and diabetes are closely related to each other as about 80% of diabetics are obese. Obesity is a common finding in type 2 diabetes. The objective of the study was to investigate the antidiabetic effects of [10]-gingerol in streptozotocin (STZ)- and HFD-induced diabetic rats.

Methods: Wistar rats were used for the study. Animals were divided into six groups. The six groups in this study were, Group I (normal control), Group II (diabetic control), Group III (glibenclamide at 5 mg/kg p.o.), Group IV (orlistat at 60 mg/kg p.o.), Group V ([10]-gingerol at 15 mg/kg p.o.), and Group VI [10]-gingerol (30 mg/kg p.o.), respectively. The antidiabetic activity was assessed using blood glucose level, body weight, and various biochemical parameters such as serum total cholesterol (TC) level, triglyceride (TG) level, high-density lipoproteins (HDLs), total protein (TP), serum alanine transaminase, and aspartate aminotransferase (serum glutamic-oxaloacetic transaminase), respectively.

Results: [10]-gingerol exhibited an antidiabetic effect by significantly decreased the level of blood glucose, body weight, TC, TG, TP, and increase HDL. The results of the study demonstrated that the treatment with [10]-gingerol significantly ($p<0.05$) and dose dependently prevented STZ- and HFD-induced diabetic rats.

Conclusions: The findings of the study suggest that [10]-gingerol possesses potential antidiabetic activity as it lowers serum glucose level.

Keywords: [10]-gingerol, Diabetes, High-fat diet, Streptozotocin.

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INTRODUCTION

The occurrence of type 2 diabetes mellitus is rapidly rising around the world's population. India is the "diabetes capital of the world" with 62.4 million Indians having type 2 diabetes in 2011 [1]. Blood glucose level was increased in type 2 diabetes mellitus due to a progressive decline in insulin action (insulin resistance) and pancreatic β-cell dysfunction [2]. A major risk factor for insulin resistance is obesity, which is generally caused by regular physical inactivity and high-fat diet (HFD) [3]. Obesity and diabetes are closely related to each other as about 80% of diabetics are obese. Obesity is a common finding in type 2 diabetes. There is impaired insulin sensitivity of peripheral tissues such as muscle and fat cells to the action of insulin in obese individuals (insulin resistance). The reduction of weight in obese patients produces an enhancement in diabetic state [4]. Obesity increases the risk of type II diabetes, cardiovascular disease, cancer, and premature death [5]. A pharmacological factor involved in obesity and diabetes includes lipoprotein lipase (LL), having a central role in the metabolism of both triglyceride (TG)-rich particles and high-density lipoproteins (HDLs). LL is determinant of serum TG and HDL concentrations [6]. The influence of obesity on type 2 diabetes risk is determined not only by the amount of obesity but also by fat deposition [7].

The current treatment for type 2 diabetes includes insulin and oral hypoglycemic drugs, i.e., sulfonylurea derivatives, thiazolidinediones, biguanides, and α-glucosidase inhibitors, but these medications have most of the side effects. Many traditional plant remedies for obesity and diabetes are used throughout the world. Ginger, the rhizome of the *Zingiber officinale* is commonly consumed dietary condiments. Ginger and its constituents show antioxidant activity and prevent the damage of macromolecules, caused by the free radicals/oxidative stress [8]. The compounds derived from natural sources, which are considered to be safe and cost effective, are needed. Ginger is one of the most widely used natural products consumed as a spice and medicine for treating nausea, dysentery, diabetes, heartburn, flatulence, diarrhea, loss of appetite, infections, cough, and bronchitis. Experimental studies showed that its active components [10]-gingerol exert antidiabetic effects against streptozotocin (STZ)- and HFD-induced diabetic rats.

METHODS

Animals

Wistar rats (150–200 g) were group housed (n=6) under a standard 12 h light/dark cycle and controlled conditions of temperature and humidity (25±2°C, 55–65%). Rats received standard rodent chow and water *ad libitum*. Rats were acclimatized to laboratory conditions for 7 days before carrying out the experiments. All the experiments were carried in a noise-free room between 08.00 and 15.00 h. A separate group (n=6) of rats was used for each set of experiments. The animal studies were approved by the Institutional Animal Ethics Committee, constituted for the Purpose of Control and Supervision of Experimental Animals by the Ministry of Environment and Forests, Government of India, New Delhi, India.

Drugs and chemicals

[10]-gingerol (Sigma-Aldrich) and STZ (Sigma-Aldrich) were used in the present study. All other chemicals and other biochemicals used in the experiments were of analytical grade from different firms.

Experimental design and treatment protocol

After 28 days of administration of HFD, the rats were injected intraperitoneally by a single dose of a prepared solution of STZ (30 mg kg suspended in 0.1 mol/L citrate buffer at pH 4.5). If the fasting blood glucose was more than 300 mg/100 ml after 72 h of STZ injection,

the diabetic type 2 models were successful. Approximately 200 µl blood was collected from each animal by retro-orbital sinus in 0.5 ml Eppendorf tubes containing 20 µl of 20% sodium fluoride solution. The collected blood was centrifuged at 8000 rpm at temperature 18–22°C for 10 min by centrifuge machine. All animals were weighed, randomized, and divided into six groups (six animals each) and were given the following treatment for 21 days by oral route [9].

- Group I – Normal
- Group II – Diabetic rats received only distilled water (negative control)
- Group III – Diabetic rats were treated with glibenclamide (5 mg/kg p.o.)
- Group IV – Diabetic rats received orlistat (60 mg/kg/day p.o.)
- Group V – Diabetic rats received [10]-gingerol (15 mg/kg/day p.o.)
- Group VI – Diabetic rats received [10]-gingerol (30 mg/kg/day p.o.)

At the end of the 21st day treatment, i.e., 24 h after the last dose of the drug and standard drugs, the rats were anesthetized and blood was collected by retro-orbital plexus followed by heart puncture and allowed to clot. After blood withdrawal, animal was sacrificed. The serum was separated by centrifugation at 3000 rpm at 4°C for 20 min for the analysis of various biochemical parameters.

Biochemical evaluation in serum

Serum total cholesterol (TC) level, TG level, HDL, total protein (TP), serum alanine transaminase (SGPT), and aspartate aminotransferase (serum glutamic-oxaloacetic transaminase [SGOT]) were determined using standard kits from Transasia Bio-Medicals Limited, Mumbai, India. The estimation procedure is obtained in detail from leaflets provided by the commercially available kits which are as follows:

Histopathology

The formalin-fixed tissue pieces from pancreas were serially dehydrated in alcohol and cleared in xylene and were embedded in paraffin blocks. The microsections (4–5 microns thick) were cut and stained in hematoxylin and eosin using the standard method and examined for histopathological changes.

Statistical analysis

All statistical analyses are expressed as the mean±standard error of the mean. Data were analyzed by one-way ANOVA, where applicable $p<0.05$ was considered statistically significant, compared with vehicle followed by Dunnett's test.

RESULTS AND DISCUSSION

Effect of [10]-gingerol on body weight in STZ- and HFD-induced diabetic rats

As represented in Table 1, body weights of animals in all groups were performed at the initial and end of the study. Body weight of animals was significantly ($p<0.05$) maintained in all treatment groups (glibenclamide 5 mg/kg p.o., orlistat 60 mg/kg p.o., and [10]-gingerol 15 and 30 mg/kg p.o. during the study as compared to the control group).

Effect of [10]-gingerol on blood glucose level in STZ- and HFD-induced diabetic rats

A blood glucose level of animals in all groups was recorded at the 0th, 8th, and 21st days. Progressive decrease in blood glucose level was found in all treatment groups during the study. At the end of experiment, glibenclamide 5 mg/kg p.o., orlistat 60 mg/kg p.o., and [10]-gingerol 15 and 30 mg/kg p.o. treated group blood glucose level decreased significantly ($p<0.05$) at the 21st day, as represented in Table 2.

Effect of [10]-gingerol on lipid profile level in STZ- and HFD-induced diabetic rats

In orlistat (60 mg/kg), glibenclamide (5 mg/kg), and [10]-gingerol 15 and 30 mg/kg p.o. treated group, i.e., TC, TG, and TP were significantly ($p<0.05$) decreased as compared with the control group as shown in Table 3. Furthermore, there was significantly ($p<0.05$) increased in HDL level in all treatment groups when compared with the control group.

Effect of [10]-gingerol on SGOT and SGPT in STZ- and HFD-induced diabetic rats

After end days of the experiment, SGOT and SGPT levels were significantly ($p<0.001$) elevated in the diabetic control group. As shown in Table 4, in [10]-gingerol 15 mg/kg and 30 mg/kg treated group, SGOT and SGPT were significantly decreased ($p<0.01$). In 5 mg/kg p.o. glibenclamide and 60 mg/kg p.o. orlistat-treated group, SGOT and SGPT were significantly decreased ($p<0.001$) as compared with the control group.

Histopathological analysis

The histopathological illustration showed normal acini and normal cellular population in the islets of Langerhans in the pancreas of vehicle-treated rats (Fig. 1a). General damage to the islets of Langerhans and reduced dimensions of islets (Fig. 1b) and restoration of the normal

Table 1: Mean body weight change

Group	Drug	Dose	Body weight (g)	
			Onset of study	End of study
I	Normal	1% Tween 80	210.15±8.83	230.18±8.93
II	Control	1% Tween 80	220.20±10.00	195.30±8.37
III	Glibenclamide	5 mg/kg p.o.	230.22±8.26	192.40±10.45
IV	Orlistat	60 mg/kg p.o.	230.17±7.09	167.40±6.59**
V	[10]-gingerol	15 mg/kg p.o.	232.15±6.00	188.20±7.50*
VI	[10]-gingerol	30 mg/kg p.o.	230.10±5.00	180.10±6.50*

Values are expressed as mean±S.E.M. (n=6). Values are statistically significant at $p<0.05$ versus control group, respectively (one-way ANOVA followed by Dunnett's test)

Table 2: Antidiabetic activity of [10]-gingerol on blood glucose level in STZ- and HFD-induced diabetic rats

Groups	Treatment	Dose	Blood glucose (mg/dl)		
			Day 0	Day 8	Day 21
I	Normal	1% Tween 80	80.00±4.00	85.00±4.00	105.00±5.00
II	Control	1% Tween 80	290.00±7.00	387.00±9.60#	398.00±10.00#
III	Glybenclamide	5 mg/kg p.o.	246.00±6.40	128.00±6.50**	115.00±5.00**
V	Orlistat	60 mg/kg p.o.	250.00±6.00	145.10±7.00*	119.00±5.80**
VI	[10]-gingerol	15 mg/kg p.o.	255.00±5.50	157.00±7.86*	140.00±6.70*
VII	[10]-gingerol	30 mg/kg p.o.	251.00±6.70	149.20±7.00*	121.00±6.50*

Values are expressed as mean±S.E.M. (n=6). Values are statistically significant at $p<0.05$ versus negative control group, respectively (one-way ANOVA followed by Dunnett's test)

Table 3: Effect of [10]-gingerol on lipid profile level in STZ- and HFD-induced diabetic rats

Group	Drug	Dose	Total cholesterol (mg/dl)	Triglyceride (mg/dl)	HDL (mg/dl)	TP (g/dl)
I	Normal	1% Tween 80	80.50±5.50	75.00±8.00	51.87±1.13	75.00±8.00
II	Control	1% Tween 80	190.0±5.00	137.5±6.50	27.48±2.87	135.50±6.50
III	Glibenclamide	5 mg/kg p.o.	115.0±5.00***	83.00±9.00**	49.78±2.03**	80.00±9.00***
IV	Orlistat	60 mg/kg p.o.	109.00±3.60***	80.00±9.00**	50.78±2.03***	83.00±5.50***
V	[10]-gingerol	15 mg/kg p.o.	130.0±5.00**	96.00±7.00*	36.10±1.90*	95.50±5.00**
VI	[10]-gingerol	30 mg/kg p.o.	121.5±4.50**	86.50±5.50*	45.00±1.37**	85.00±7.00***

Values are expressed as mean±S.E.M. (n=6). Values are statistically significant at $P<0.05$ (one-way ANOVA followed by Dunnett's test)

Table 4: Effect of [10]-gingerol on SGOT and SGPT in STZ- and HFD-induced diabetic rats

Group	Drug	Dose	SGOT (IU/L)	SGPT (IU/L)
I	Normal	1% Tween 80	57.00±5.00	45.00±5.00
II	Control	1% Tween 80	120.5±7.50	115.0±10.00
III	Glibenclamide	5 mg/kg p.o.	68.50±4.50**	58.00±4.00**
IV	Orlistat	60 mg/kg p.o.	63.50±4.50**	55.00±4.00**
V	[10]-gingerol	15 mg/kg p.o.	78.50±5.50*	70.50±2.50*
VI	[10]-gingerol	30 mg/kg p.o.	70.50±5.50*	62.50±6.50**

Values are expressed as mean±S.E.M. (n=6). Values are statistically significant at p<0.05 (one-way ANOVA followed by Dunnett's test). SGOT: Serum glutamic-oxaloacetic transaminase

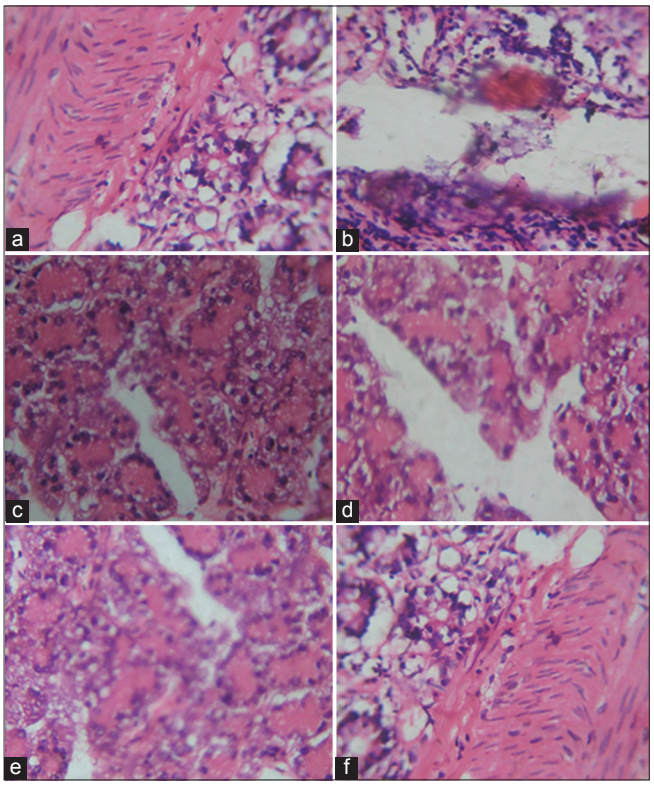

Fig. 1: Effect of drugs on pancreatic histopathology of diabetic rats (a) Normal, (b) control, (c) glibenclamide, (d) orlistat, (e) [10]-gingerol (15 mg/kg), (f) [10]-gingerol (30 mg/kg)

cellular population size of islets with hyperplasia by glibenclamide (Fig. 1c) were also shown. The partial restoration of the normal cellular population and enlarged size of β-cells with hyperplasia were shown by [10]-gingerol (15 and 30 mg/kg; Fig. 1d-f).

In the present study, the effects of [10]-gingerol on diabetes were assessed using STZ- and HFD-induced diabetic rat model. The administration of [10]-gingerol for 21 days resulted in a significant reduction in blood glucose levels and lipid profile. The observed antihyperglycemic effect of [10]-gingerol is supported by our previous report of ginger [10].

The data obtained from this study showed that the treatment of [10]-gingerol, glibenclamide, and orlistat protects the diabetic rats from massive body weight loss when given orally. [10]-gingerol, glibenclamide, and orlistat-treated rats showed a recovery in final body weight which was close to that of normal control rats. Moreover, the weight gain was lesser in the diabetic rats when compared ($p<0.05$) to normal control rats. Thus, the body weight loss due to catabolic effects seen in diabetic rats was only partially attenuated by all treatment groups, respectively. The decrease in body weight in diabetic rats could be due to dehydration and catabolism of fats and proteins [11].

Reports concerning the role of [10]-gingerol in connection with blood glucose level are not available in literature and our study is the first to report that [10]-gingerol attenuates the effect of blood glucose level. The blood glucose levels observed in the present study revealed a significant effect of [10]-gingerol on blood glucose level in STZ- and HFD-induced diabetic rats during the 3 weeks of the treatment period. Diabetic rats had significantly lowered ($p<0.01$) blood glucose levels, whereas [10]-gingerol-treated diabetic rats had significantly ($p<0.01$) increased blood glucose levels.

[10]-gingerol treatment was able to improve the lipid profile in STZ- and HFD-induced diabetic rats. Results of the histopathological changes in STZ- and HFD-induced type 2 diabetic rats, such as hepatic lipid accumulation and fatty degeneration, are consistent with the results of the lipid profile level. Treatment of diabetic rats with [10]-gingerol showed a considerable reduction in hepatic lipid accumulation. Lipase functions as a lipolytic enzyme that hydrolyzes TGs and phospholipids in circulating plasma lipoproteins. Reduction of fat absorption by the inhibition of pancreatic lipase is known to be beneficial for the regulation of obesity and related metabolic disorders [12].

The increase in blood sugar is accompanied by the increase in TC, TG, LDL, very low-density lipoprotein (VLDL), and fall of HDL. It is well known that in uncontrolled type 2 diabetes mellitus, there will be an increase in TC, TG, LDL, VLDL, and TG with a decrease in HDL which contributes to the coronary artery disease [13]. However, the treatment of [10]-gingerol associated with reduced the elevated levels of TC, TG, LDL, and VLDL as compared to control in diabetic animals at the 21st day. There was an increase in HDL also, which indicates that [10]-gingerol may be beneficial to diabetic individuals with atherosclerosis since superior HDL level is associated with the lowered risk of the development of atherosclerosis in diabetes mellitus [14].

Oral administration of [10]-gingerol for 21 days to diabetic rats decreased their food consumption and improved body weight. This could be due to better control of the hyperglycemic state in the diabetic rats. Decreased blood glucose could improve body weight in STZ- and HFD-induced diabetic rats. During diabetes mellitus, the excess glucose present in the blood leads to glycation of tissue proteins [15,16]. Administration of [10]-gingerol to diabetic rats significantly ($p<0.05$) decreased the level of blood glucose. In diabetes mellitus, a variety of proteins are subjected to non-enzymatic glycation and this is thought to contribute to the long-term complications of the disease [17].

Diabetes mellitus is also associated with hyperlipidemia with a profound alteration in the concentration and composition of lipid [18]. Changes in the concentrations of the lipid with diabetes mellitus contribute to the development of vascular disease [19,20]. Fatty acids, an important component of cell membranes, are eicosanoid precursors and are, therefore, required for both the structure and function of every cell in the body [21]. STZ was significantly increased TL, TC, TG, FFA, phospholipids, LDL, and VLDL levels. The abnormally high concentration of serum lipids in diabetes mellitus is mainly due to an increase in the mobilization of free fatty acids from the peripheral fat depots since insulin inhibits the hormone-sensitive lipase. The marked hyperlipidemia that characterizes the diabetic state may, therefore, be regarded as a consequence of the uninhibited actions of lipolytic hormones on the fat depots [22]. Excess of fatty acids in the plasma produced by STZ promotes the liver conversion of some fatty acids to phospholipids and cholesterol.

Administration of [10]-gingerol to STZ- and HFD-induced diabetic rats produced a significant reduction in serum lipid profile, suggesting its potential in the prevention of hyperlipidemia and obesity. During the experimentation, Wistar rats did not show any mortality or any other adverse effects when the rats fed orally with [10]-gingerol at the doses of 15 and 30 mg/kg. Thus, the [10]-gingerol has a good periphery of safety. Furthermore, all diabetic-treated groups showed histopathological changes of varying degree of alveolar histiocytosis due to phospholipidosis.

Diabetes is the second most common cause of death and different types of oral hypoglycemic agents are available for its treatment but none offers complete glycemic control. The side effect of taking insulin and oral hypoglycemic agents has brought about a growing interest for alternative traditional herbal medicine [23]. Herbal medicine is prepared from various plant parts to contain many bioactive compounds used primarily for treating [24]. The present study showed that [10]-gingerol exhibits significant insulin secretion and β-cells regeneration as well as antioxidant activity in experimental rats. Thus, a sufficient supply of antioxidants may prevent or delay β-cells dysfunction in diabetes by protecting against glucose toxicity. Moreover, antioxidant activity regulates glucose homeostasis through a multitude of actions. Further studies are in progress to isolate the active principle and elucidate the exact mechanism of the action of [10]-gingerol.

CONCLUSIONS

The findings indicated that the usefulness of the [10]-gingerol STZ- and HDF-induced diabetic rats. Our study suggested that [10]-gingerol dose dependently produced antidiabetic activity. This study might be helpful to understand the role of [10]-gingerol in the clinical treatment of diabetes mellitus.

AUTHORS' CONTRIBUTIONS

The authors declare that this work was done by the author named in this article.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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