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Original article

Kaempferol, a flavonoid, ameliorates hyperglycemia by attenuating the key enzymes of carbohydrate metabolism in streptozotocin-induced experimental diabetic rats

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Summary. Diabetes mellitus is a chronic metabolic disease with the highest rates of prevalence and mortality worldwide that is caused by an absolute or relative lack of insulin and/or reduced insulin activity, which results in hyperglycemia and abnormalities in carbohydrate, protein, and fat metabolism. The aim of this study was to investigate the effect of kaempferol on hepatic key enzymes of carbohydrate metabolism in streptozotocin-induced diabetic rats. An optimum dose of kaempferol (100 mg/kg body weight) was orally administered for 45 days to streptozotocin-diabetic rats for the assessment of glucose, insulin, hemoglobin (Hb), glycated hemoglobin (HbA1c), hepatic glycogen, and activities of carbohydrate metabolizing enzymes, such as glucokinase, glucose 6- phosphatase, fructose 1, 6-bisphosphatase and glucose-6-phosphate dehydrogenase in normal and streptozotocin-diabetic rats. Kaempferol at 100mg dose produced similar effects on all biochemical parameters studied as that of glibenclamide (600 mg/kg BW), a standard drug. These results showed that kaempferol has potential antihyperglycemic activity in streptozotocin-induced diabetic rats.

Key words: diabetes mellitus, streptozotocin, glibenclamide, kaempferol, antihyperglycemic.

Introduction

Diabetes is a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both. The chronic hyperglycemia of diabetes is associated with long-term damage, dysfunction, and failure of different organs, especially the eyes, kidneys, nerves, heart and blood vessels (1). Recent studies indicate that there are 171 million people in the world with diabetes in the year of 2000 and this is projected to increase to 366 million by 2030 (2). As an insulin-dependent tissue that plays a pivotal role in glucose and lipid homeostasis, the liver is severely affected during diabetes mellitus (3, 4). Deterioration of insulin control exacerbates metabolic disturbances by altering the activities of key enzymes, such as glucokinase (GK), phosphofructokinase (PFK), pyruvate kinase (PK), pyruvate carboxylase (PCB), fructose-1, 6-bisphosphatase (FBPase), phosphoenolpyruvate carboxykinase (PEPCK), and glucose-6-phosphatase (G-6-Pase), in the diabetic liver. These changes impair peripheral glucose utilization and augment hepatic glucose production (5-7). Therefore, regulators of hepatic glucose metabolism are potentially excellent targets in the treatment of type II diabetes mellitus.

Kaempferol (Figure 1), a flavonoid, naturally occurs in a variety of fruits, vegetables, wine, and tea. It can be isolated from tea, broccoli, witch-hazel, propslis, grapefruit, and other plants (8). The medicinal properties of kaempferol include antioxidant, anti-inflammatory, and anticancer activities (9-11). Several studies have shown that intake of foods containing kaempferol is associated with reductions in mortality, the incidence of myocardial infarction, and the incidence of cerebrovascular disease, as well as with

a slightly reduced risk of coronary heart disease (12-14). Previously, in an in vitro study, it was shown that kaempferol ameliorates hyperglycemia by improving insulin-stimulated glucose uptake in adipocytes (15). Kaempferol also performs a beneficial role in diabetes by preventing oxidative damage in pancreatic β-cells (16).

In our previous study, the kaempferol at an optimum dose of 100 mg decreased plasma glucose level and improved body weight in a 45-day study (17) and also kaempferol exhibited hypolipidemic action (17) and antioxidant properties (18), and glycoprotein components (19), membrane-bound ATPases (20) prevent mitochondrial damage (21) in streptozotocin (STZ)-diabetic rats. So far no study has been conducted on the effect of kaempferol on carbohydrate metabolic enzymes in STZ-induced diabetic rats. Hence, in the present study we have sought to examine the effects of kaempferol on carbohydrate metabolic enzymes in STZ-induced diabetic rats.

The structure of kaempferol is depicted in Figure 1.

Materials and methods

Drugs and chemicals

STZ and kaempferol were purchased from Sigma-Aldrich (St. Louis, MO). All other chemicals were of analytical grade. Experimental animals Male albino rats of Wistar strain of body weight (BW) ranging from 180 to 200 g were procured from Central Animal House, King Saud University, and they were maintained in an air-conditioned room (25±1°C) with a 12 h light/dark cycle. The animals were fed *ad libitum* with normal laboratory pellet diet used in the study and procedures involving animals and their care were accordance with the Policy of Research Centre, King Saud University.

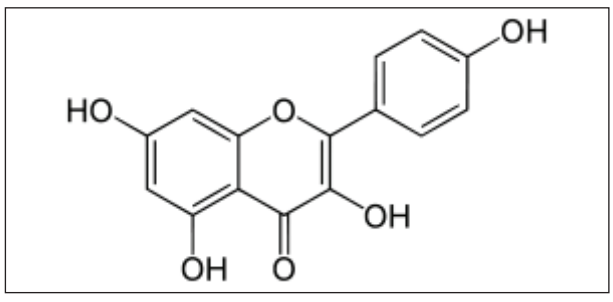

Figure 1. Structure of the kaempferol

Experimental induction of diabetes

The animals were made diabetic by a single intraperitoneal injection of streptozotocin (STZ, 40 mg/kg BW, between 8:00 am and 9:00 am) in a freshly prepared citrate buffer (0.1 M, pH 4.5) after an overnight fast. STZ-injected animals were given 20% glucose solution for 24 h to prevent initial drug-induced hypoglycemic mortality (22). Diabetes was confirmed by measuring the fasting plasma glucose concentration 96 h after induction. Albino rats with a plasma glucose level above 220 mg/dL were considered diabetic and were used in this experiment.

Experimental design

The animals were randomly divided into five groups consisting of six animals each. Kaempferol or glibenclamide was dissolved in 5% DMSO and administered by intubation (p.o.) once a day, between 9 am and 10 am, for 45 d. The oral LD50 value of kaempferol was reported at 980 mg/kg in rats (23). Therefore, in our previous studies, we have chosen 50, 100, and 200 mg/kg doses of kaempferol for testing the glucose lowering action (17), which is relatively safe and can achieve the maximum protective activity in STZ-induced diabetic rats. Of the three doses of kaempferol (50, 100, and 200 mg/kg BW), 100 mg gave the maximum improvement in plasma glucose and insulin (17). Hence, the active dose of 100 mg was used in this study:

- Group I: normal control rats (5% DMSO alone)
- Group II: normal rats + kaempferol (100 mg/kg BW)
- Group III: diabetic control
- Group IV: diabetic rats + kaempferol (100 mg/kg BW)
- Group V: diabetic rats + glibenclamide (600 mg/kg BW)

Glibenclamide is a sulfonylurea antidiabetic agent, a class of drugs used to treat type II diabetes mellitus. This disease is a chronic metabolic illness characterised by a deficiency of insulin, a hormone produced by the pancreas which controls the sugar in the blood. For that, in this study we are using glibenclamide as

a standard drug for the comparison of efficacy with kaempferol-treated diabetic rats (22).

After 45 days of treatment, the animals were fasted for 12 h, anaesthetized between 8:00 a.m. to 9:00 a.m. Each morning using ketamine (24 mg/kg body weight, intramuscular injection), and sacrificed by decapitation. Blood was collected from the tail and it's in a dry test tube and allowed to coagulate at ambient temperature for 30 min. Blood was collected in tubes with a mixture of potassium oxalate and sodium fluoride (1:3) for the estimation of plasma insulin, glucose, and with ethylenediamine tetra acetic acid (EDTA) for the estimation of hemoglobin, glycated hemoglobin. Liver and kidney were immediately dissected out, washed in ice-cold saline to remove the blood. Tissues were sliced into pieces and homogenized in an appropriate buffer (pH 7.0) in cold condition to give 20% homogenate (w/v). The homogenates were centrifuged at 1000 rpm for 10 min at 0°C in cold centrifuge. The supernatants were separated and used for various biochemical estimations.

Biochemical analysis

Plasma glucose was estimated by the method of Trinder using a reagent kit (24). Hemoglobin (Hb) and glycated hemoglobin (HbA1c) were estimated by the method of Drabkin & Austin (25) and Sudhakar & Pattabiraman (26), respectively. The plasma insulin in the rat was measured by the method of Burgi et al. (27). Glucokinase, glucose 6-phosphatase, fructose 1,6-bisphosphatase and glucose-6-phosphate dehydrogenase were assayed in the tissues by the methods of Brandstrup et al. (28), Koide & Oda (29), Gancedo & Gancedo (30) and Bergmeyer (31), respectively. Glycogen content was determined as described by Morales et al. (32).

Statistical analysis

Values were given as means ± standard deviation (SD) for six rats in each group. Data were analyzed by one-way analysis of variance followed by Duncan's Multiple Range Test (DMRT) using SPSS version 11 (SPSS, Chicago, IL, USA). The limit of statistical significance was set at $p < 0.05$.

Results

The effects of kaempferol on body weight and plasma glucose in diabetic rats are depicted in Figure 2. The plasma glucose level elevated and bodyweight decreased significantly in diabetic rats. Treatment with kaempferol at a dose of 100mg/kg/body weight/day lowered the plasma glucose and elevated body weight significantly; 100 mg dose improved the plasma glucose level towards normalcy and elevated body weight significantly.

The levels of plasma insulin, Hb, and HbA1c are given in Table 1. Plasma insulin and Hb decreased and HbA1c increased significantly in diabetic rats, and these values improved towards normalcy on treatment with kaempferol.

The activities of carbohydrate metabolic enzymes and level of glycogen in the liver of diabetic rats are given in figure 3. The decreased activities of glucokinase and glucose 6-phosphate dehydrogenase and level of glycogen observed in the liver of diabetic rats improved towards normalcy on treatment with kaempferol.

Changes in the activities of gluconeogenic enzymes in the liver and kidney of diabetic rats are shown in figure 4 and 5. Increased activities of glucose 6-phosphatase and fructose 1, 6-bisphosphatase were observed in the liver and kidney of diabetic rats, and these activities decreased on treatment with kaempferol.

Discussion

Diabetes mellitus is a disease due to abnormality of carbohydrate metabolism and it is mainly linked with less insulin level or insensitivity of target organs to insulin (33). Type 2 diabetes is the consequence of a number of defects, including impaired insulin secretion by the pancreatic βcell, resistance of peripheral tissues to the glucose-utilizing effect of insulin, and improved hepatic glucose production (34). Streptozotocin-induced diabetes is characterized by a severe loss in body weight (35), which might be the result of protein wasting due to unavailability of carbohydrate as an energy source (36). Oral administration of kaempferol improved the body weight in diabetic rats, which

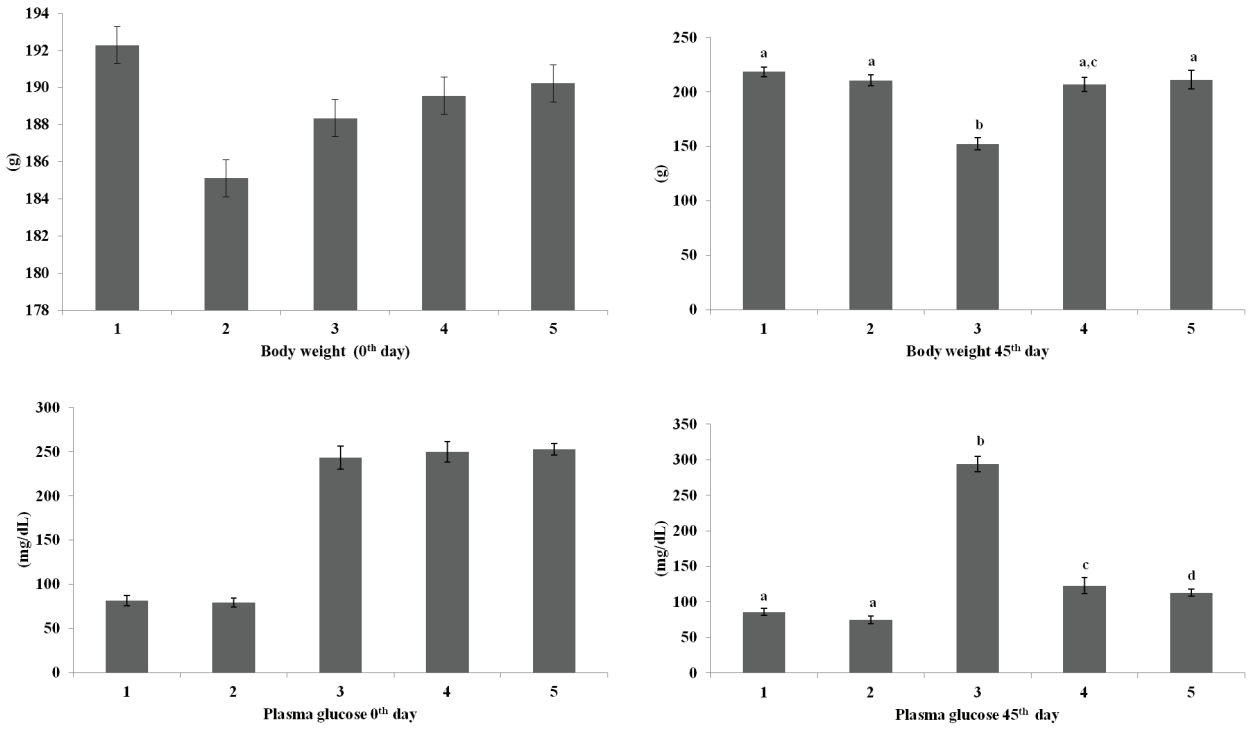

Figure 2. Effect of kaempferol on body weight and plasma glucose in STZ-diabetic rats

Table 1. Effect of kaempferol on plasma insulin, haemoglobin and glycosylated haemoglobin in STZ-diabetic rats

Groups	Insulin (mU/mL)	Haemoglobin (g/dL)	Glycosylated haemoglobin (mg/g of Hb)
Control	16.11 ± 1.19[a]	15.02 ± 1.09[a]	0.45 ± 0.02[a]
Control + kaempferol (100 mg/kg BW)	17.03 ± 0.98[a]	14.56 ± 1.28[a]	0.41 ± 0.03[a]
Diabetic control	6.38 ± 0.51[b]	6.95 ± 0.51[b]	1.21 ± 0.01[b]
Diabetic + kaempferol (100 mg/kg BW)	12.85 ± 0.94[c]	11.83 ± 0.90[c]	0.56 ± 0.04[c]
Diabetic + glibenclamide (600 mg/kg BW)	13.79 ± 1.23[c]	13.34 ± 1.02[a,c]	0.50 ± 0.02[d]

Values are given as means ± S.D. for six rats in each group.
Values not sharing a common superscript differ significantly at p < 0.05. Duncan's Multiple Range Test (DMRT).

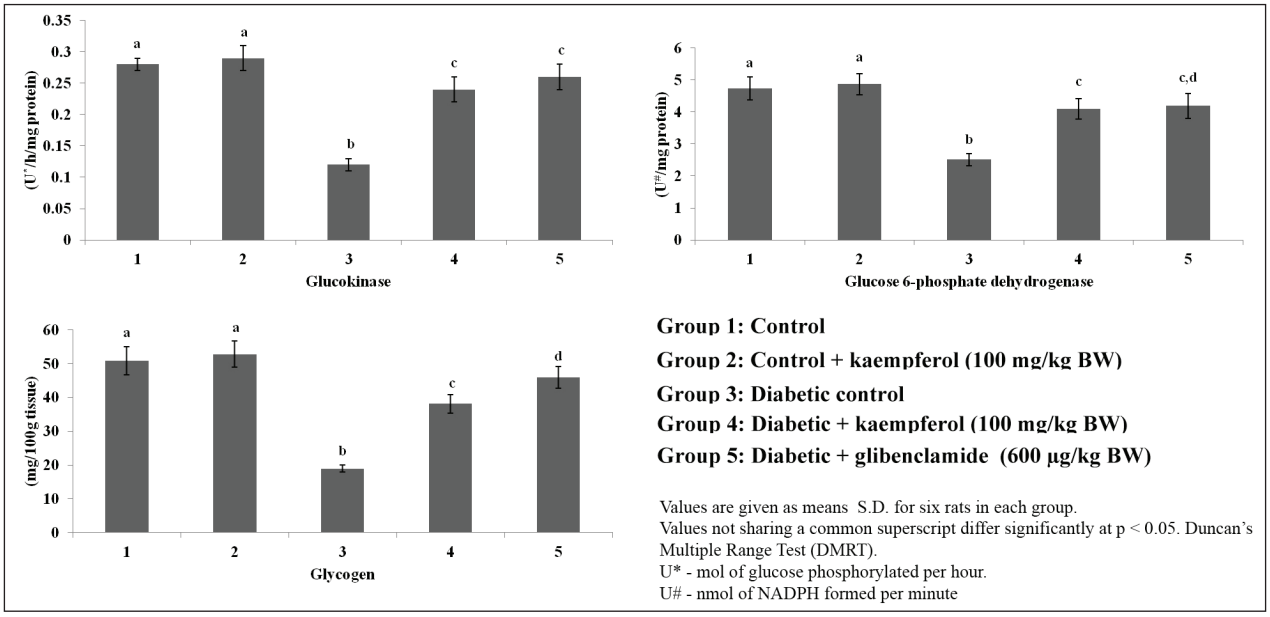

Figure 3. Effect of kaempferol on glucokinase, glucose 6-phosphate dehydrogenase activities and glycogen content in the liver of STZ-diabetic rats

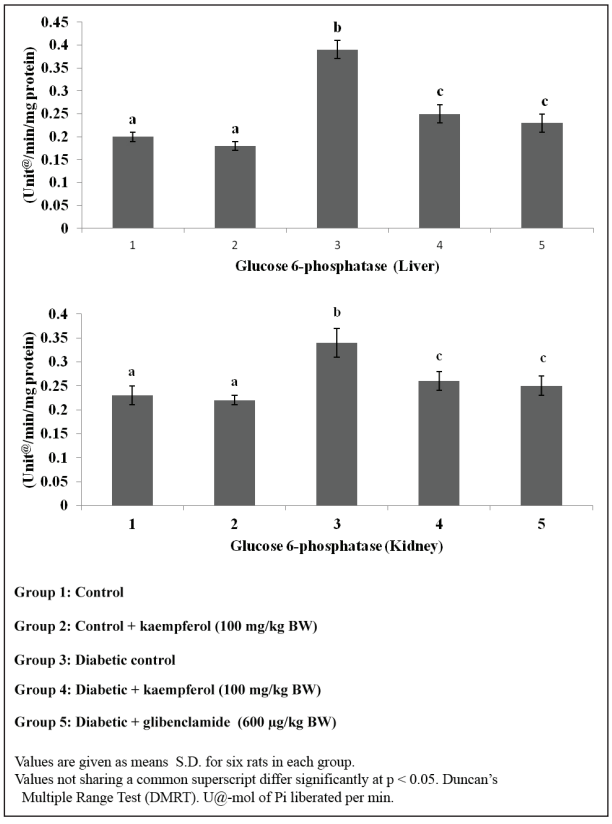

Figure 4. Effect of kaempferol on glucose 6-phosphatase activities in the liver and kidney of STZ-diabetic rats

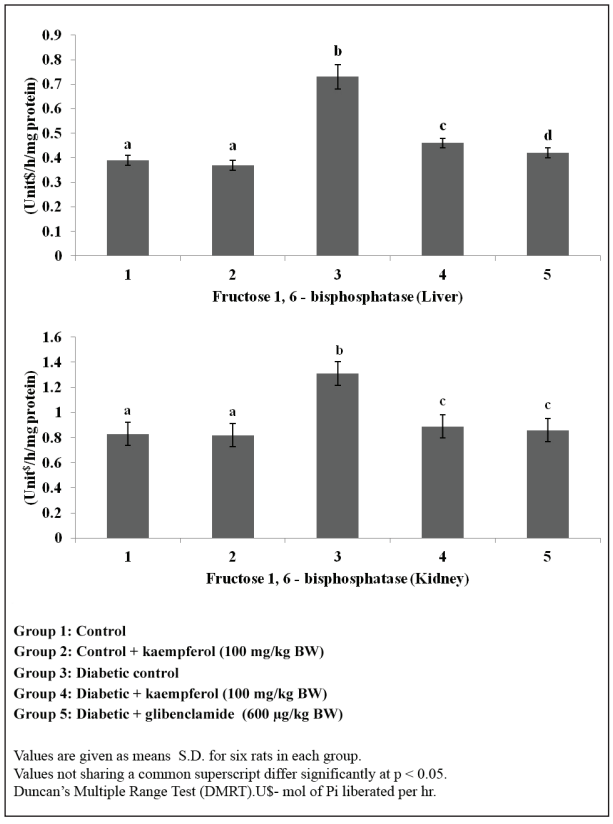

Figure 5. Effect of kaempferol on fructose 1, 6-bisphosphatase activities in the liver and kidney of STZ-diabetic rats

might be via glyceamic control. In our previous study Khalid et al reported that (17), studied on kaempferol, reported an increase of body weight and decreased the plasma glucose in streptozotocin-diabetic rats after receiving 100 mg kaempferol. The decrease in plasma glucose level of diabetic rats treated with kaempferol might be due to elevated secretion of insulin, which in turn, increases the utilization of glucose by the tissues. Previously in vitro study was observed that kaempferol to ameliorate hyperglycemia by improved insulin stimulated glucose uptake in adipocytes (37).

Plasma insulin increased significantly in diabetic rats, and these values improved towards normalcy on treatment with kaempferol. The observed increase in the levels of plasma insulin indicates that kaempferol stimulates insulin secretion by the closure of K+-ATP channels, membrane depolarization and stimulation of Ca2+ influx, an initial key step in insulin secretion from the remnet β-cells or from regenerated β-cells.

Decrease the levels of total hemoglobin are observed in diabetic rats might be due to the increased formation of HbA1c. Hyperglycemia is the clinical hallmark of poorly controlled diabetes, which is known to cause glycation, and also known as non-enzymatic glycosylation. HbA1cwas found to increase in patients with diabetes mellitus and the increase was directly proportional to the fasting blood glucose levels (38). Oral administration of kaempferol showed a significant decline in HbA1c indicates the efficiency of kaempferol in glycemic control.

Glycogen is the primary intracellular storable form of glucose and its level in various tissues is a direct reflection of insulin activity as insulin promotes intracellular glycogen deposition by stimulating glycogen synthase and inhibiting glycogen phosphorylase (39). The liver glycogen content is markedly decreased in diabetic animals (40), which are in proportion to insulin deficiency (41). Diabetic rats treated with kaempferol brought back liver glycogen to near normal level, which could be due to increased secretion of insulin.

Glucokinase, is the rate-limiting enzyme in the catabolism of glucose, which phosphorylates glucose to glucose-6-phophate and is known to be changed in diabetic state (42). Glucokinase is both insulin dependent and an insulin sensitive enzyme and is almost completely inhibited or inactivated in the diabetic rat liver in the absence of insulin (43). Glucokinase insufficiency in diabetic rats can cause decreased utilization of glucose for energy production (44). In this study, glucokinase activity significantly decreased in the liver of diabetic rats which might be due to a deficiency of insulin and treatment with esculetin increased insulin secretion, which in turn, elevated the activity of glucokinase. Increased glucokinase activity leads to decrease in blood glucose level by utilization of glucose.

Activity of glucose 6-phosphate dehydrogenase were decreased in diabetic control rats. The decrease in the activity of this enzyme in diabetic condition may result in the diminished functioning of hexose monophosphate shunt and thereby decreasing the production of reducing equivalents such as NADH and NADPH. Insulin is reported to increase the activity of glucose 6-phosphate dehydrogenase in a dose dependent manner (45). In our study, administration of kaempferol increased the activity of glucose 6-phosphate dehydrogenase significantly by enhancing insulin secretion.

The hepatic gluconeogenic enzymes i.e. glucose-6-phosphatase and fructose-1,6-bisphosphatase were significantly increased in the liver of diabetic rats (46), may be due to deficiency of insulin enhances the activities of gluconeogenic enzymes resulting endogenous glucose production may be contributing to the increased glucose released from the liver. Diabetic rats treated with kaempferol controlled the activities of these enzymes, either may be regulation of metabolic activation or inhibition of glycolysis and gluconeogenesis. These results consecutively proved that kaempferol normalizes the disturbed glucose metabolism by decreasing hepatic glucose production through insulin release.

Conclusion

The administration of kaempferol results in a significant restoration of the plasma glucose, insulin, Hb, HbA1c, and key enzymes of carbohydrate metabolism. The present study reveals that kaempferol exhibits significant ameliorative potential by modulating the glycolytic enzymes thereby controls the glucose metabolism in experimental diabetic rats.

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