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IJBPAS, May, 2017, 6(5): 918-930

ISSN: 2277–4998

International Journal of Biology, Pharmacy and Allied Sciences (IJBPAS)

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ANTIDIABETIC EFFECT OF ETHANOLIC EXTRACT OF *TRAGANUM NUDATUM* ON ALLOXAN INDUCED DIABETICS WISTAR RATS

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Received 25th Nov. 2016; Revised 30th Dec. 2016; Accepted 3rd March 2017; Available online 1st May 2017

ABSTRACT

Traganum nudatum (*T. nudatum)* is a medicinal plant widely used in folk medicine. In this study, we have undertaken the biological effects of *T. nudatum* ethanolic whole plant extracts in alloxan induced diabetic rats. Sixty albino rats (260 g) were used in this experiment and divided into six groups. Diabetes was induced in five rat groups by a single intraperitoneal injection of alloxan (150 mg/kg body weight). After hyperglycemia was confirmed, one group was considered as diabetic control and one group was treated with Glibenclamide (10 mg/kg body weight/ daily) where the remaining three groups received daily treatments with three different doses of *T. nudatum* extract (100, 200, and 400 mg/kg body weight) for 21 days each dissolved in 1 ml distilled water was administered intraperitoneally to each corresponding rat group. Blood serum biochemical markers such as urea, creatinine, cholesterol, and total serum protein levels were recorded after the treatment ended. Findings indicate that treatment with medium and high doses of *T. nudatum* extract (200 and 400

mg/kg/ body weight) reduces blood sugar values to significant levels (P<0.001) The study concluded that ethanolic extracts of *T. nudatum* treatment exhibits a significant antihyperglycemic effect without altering the body weight and can correct some biochemical markers induced by diabetes in a similar manner or better than to Glibenclamide in alloxan-induced diabetic wistar rats.

Keywords: Alloxan, Diabetes, Medicinal plants, *Traganum nudatum*, Blood glucose, Antihyperglycemic effect, Biochemical markers, Glibenclamide

1. INTRODUCTION

Diabetes mellitus is a standout amongst the most well-known metabolic disorders around the world. It is a syndrome of chronic hyperglycemia due to relative insulin deficiency, resistance, or both [1]. Prevalence rates of diabetes mellitus have been on the increase throughout the world to an extent that the condition is considered to have reached an epidemic proportion in many countries.

For diabetes treatment, numerous oral hypoglycemic inhibitors agents such as thiazolidines, meglitinides, sulfonylureas, α-glucosidase and D-phenylalanine are additionally applied with insulin and accompanied by a suitable diet and exercise [2]. In any case, none can be named as perfect, because of their side effects toxicity and the possibility of response diminution after continued usage [3]. These boundaries and adverse effects that are related to the synthetic oral hypoglycemic agents have necessitated researchers to look for newer drugs. Therefore, it has been found that natural substances extracted from plants parts and materials can offer an alternative source for antidiabetic and antioxidant agents according to their traditional medicinal implications.

Traganum nudatum Del (Chenopodiaceae) is a native halophytic shrub in arid zones of the Mediterranean basin. Extreme conditions of high temperatures, salinity and aridity can be tolerated by these species [4]. In many areas of the world, halophytes are essential sources of animal food, particularly in arid and semiarid climates. Feed shortages can be alleviated by such species which can also fulfil the feed gaps during dearth periods, when the growth limitation or dormancy of annual grassland is observed due to unsuitable conditions [5].

Traganum nudatum known locally as 'Damran' is traditionally applied in medicine to treat some diseases such as Diarrhea, wounds, rheumatism, dermatosis , gastric problems, pruritus and pimples [6]. The dried plant, crushed into a powder, used to be added to tobacco. From the

ashes of the burnt plant, sodium carbonate used to be extracted to make soap and glass. The plant is useful fodder, particularly appreciated by camels. This study was designed to evaluate the efficacy of ethanolic extracts of *T. nudatum* whole plant in reversing the hyperglycaemia in alloxan induced diabetic rats, compared to a standard anti-diabetic drug, as well.

2. MATERIALS AND METHODS

2.1 Plant material

During the flowering stage in Al-Madinah Al-Munawwarah, fresh aerial parts of *T. nudatum* (chenopodiaceae) were collected. Prof. Soliman Haroun from Floriculture and Medicinal plants, Department of Biology, Faculty of Science, Taibah University, Al-Madinah Al-Munawwarah, Saudi Arabia established the identity of the plants. The sample preparation and extraction was conducted using ethanolic extract T. nudatum which was prepared by soaking 100 g air dried powder of aerial plant parts in 1 L of 70% ethanol at 45 ºC for 2 days. Next, to remove particulate matters the mixture was filtered and lyophilized. This resulted in a powder of (22 g) which was stored at -20 °C until usage [7].

2.2 Phytochemical Screening:

Samples of *T. nudatum* roots, stems and leaves were screened phytochemically for the existence of secondary metabolites using the standard methods [8,9]. The secondary metabolites were screened for alkaloids, tannins, saponins, anthraquinones, flavonoids, Sterols, triterpenes, Steroid derivatives and cardenolides.

2.3 Determination of LD_{50}

The calculation of LD_{50} displays the potential acute toxicity of plants dose which can be lethal to 50% of any rats group [10]. In this experiment, the LD_{50} in rats was experimented to evaluate the suitable dose that should be applied. Thus, 24 albino rats were dispersed into 4 different groups each one contained 6 rats (300 g). Each dosage of ethanolic extract of *T. nudatum* viz., 200, 400, 600, 1000, 3000, 4000 and 5000 µg was dissolved in a 0.2 mL of a normal brine solution of 0.9% NaCl and directed intraperitoneally to every corresponding rat in a group. Then, in transparent plastic cages rats were housed and monitored for any toxic symptoms under temperature control (24°C) for 24 h. The quantity of dead rats was counted in every group after 24 h and the mortality percentage was determined. Six controlled rats which received only 1 mL of distilled water through an intraperitoneal infusion were compared with treated rats under the same experimental condition.

2.3 Experimental animal

Before the experiments were initiated on animals an ethical approval was acquired from the Institutional Animal Care and Use Committee (IACUC). Sixty mature of male Wistar rats (Rattus norvegicus) that weigh 250-270 g were offered by the animal house. They were kept in polypropylene cages (47x34x20cm) lined with wood shaving, and preserved under restrained environmentally friendly conditions with relative humidity (45-55%), temperature (20±2 EC) and 12 hours light/dark cycle. All rats were fed, under strict hygienic conditions and set criteria, with water ad libitum and rodent pellet diet after a week of acclimatization [11]. The normal blood sugar's level in fasting rats is 80 mg/dl that was evaluated in all rats after 16h deprivation from food using tail vein puncture. All rats during this time had access to water.

Subsequently, one single intraperitoneal dose of 150 mg/kg body weight alloxan monohydrate (Sigma-Aldrich, U.S.A) induced diabetes in 50 rats, then reconstituted in normal saline, pH 7. Hyperglycemia was established after 5 days and it has been found that the concentrations of blood sugar in measured rats were exceeding 250 mg/dl [12]. Treatment for 21 days (after diabetes induction) was conducted every day via oral administration of *T. nudatum and* Glibenclamide [13], by applying animal feeding intubation needle (Popper and Sons, New York). The rats were arbitrarily distributed into six various groups, for each having ten rats as following:

Group 1: Normal rats (No diabetes induction, no treatment).

Group 2: Diabetic rats but untreated

Group 3: Diabetic Rats + Tabs Glibenclamide 10mg/kg body weight

Group 4: Diabetic rats + *T. nudatum* extract only (100mg/Kg body weight)

Group 4: Diabetic rats + *T. nudatum* extract only (200mg/Kg body weight)

Group 4: Diabetic rats + *T. nudatum* extract only (400mg/Kg body weight)

Both rats of group A (normal nondiabetic control) and group B (diabetic control) were kept in isolated cages with an ad libitum access to food and water. All rats groups that under treatment had a daily treatment of oral doses beside unrestricted access to water and normal diet. Blood glucose concentrations and body weight were determined on the 7th, 14th and 21th day of the treatment. After the completion of treatment, rats were anesthetized and left overnight in order to estimate the biochemical parameters. In addition, blood samples were collected from all rats using cardiac puncture.

Estimation of blood glucose

Using a special cylindrical device of glucometer (Infopia Co. Ltd 891, South Korea), the collected blood samples were introduced and the blood glucose concentration was determined. The procedure was conducted by placing the rat into the cylindrical apparatus where the rat tail remained outside the cylinder. Then the tip of the tail was cut off by locking the cylinder to obtain a blood sample that was positioned on the glucometer strip and thus measuring the blood glucose concentration. After 12 h of fasting, from the completion time of the experiment, chloral hydrate was used to anesthetize animals via intra-abdominal approach. To avoid circadian in total groups, animals were sacrificed at the same period of the day.

Cardiac puncture was used to collect blood samples when after 30 min from collection they were centrifuged at 2000×g for 15 min and stored at -20 EC until usage. The liver, heart and aorta were gathered and then washed from fats. Then, they were adhered to the connective tissue, weighed and kept at a proper storage condition at -20 ºC until usage. To obtain serum blood samples were centrifuged at 3000 rpm for 15 min.

Hematological analyses

In bottles contain anticoagulant such as ethylenediaminetetraacetic acid (EDTA), the pooled blood from each group of all animals was added. In all groups of rats (n=6), the composition of hematological of the blood samples was determined including white and red blood cells which were determined by Neubauer counting Chamber. Measurement of hemoglobin was adopted using Drabkin's solution (Drabkin's Cynmetheglobin method by Fisher's Haemo-photometer). Also, packed cell volume (PCV) was estimated [14].

Biochemical analyses

Blood was centrifuged for 30 min at 6,000 rpm and then the serum was separated. After that the serum was used to determine triglycerides, total cholesterol, serum aspartate aminotransferase (AST), serum creatine kinase (CK), serum alanine aminotransferase (ALT), serum creatine, lactate dehydrogenase (LDH), creatinine, total protein and blood urea by means of kits commercially available from Randox (Crumlin, U.K.). The uv-vis spectrophotometer (Milton Roy, Spectronic-601 Spectrophotometer USA) was used to measure the parameter concentrations. Tests were carried on the Department of Physiology and Biochemistry.

2.5 Body and organ weights

Measurement of body weight changes (Δwt) of rats in each group were calculated and expressed in percentage (%) as shown:

(Body weight on day 21 body weight on day1)/(Body weight on day 1) *100. The

absolute liver weight of each rat group was measured using an electronic weighing balance, from which the relative liver weight per 100 g body weight of rat was calculated according to the following equation : [Weight of rat liver (g)/body weight on day 21 (g)] 100.

2.7. Statistical analysis:

Statistical Package of Social Sciences (SPSS), version 17 program was used to analyse data which expressed as mean ± SEM (Chicago, IL, USA). Comparisons between groups for all parameters were conducted using Dunnat's multiple comparison tests followed by one-way analysis of variance (ANOVA) [15]. The reported P values were two-tailed ($P < 0.05$) considered significant.

3. RESULTS

3.1. Phytochemical study

Qualitative phytochemical screening of the extracts of *T. nudatum* demonstrated the presence of Alkaloids, tannins, saponins and flavonoids while anthraquinones, cardinolides, Sterols and triterpenes were absent.

3.2. LD50 for *T. nudatum*

It was noted that rats which had received extract amounts of 0, 250, 500, 1,000, 2,000, 3,000, 4,000 and 5,000 mg/kg of *T. nudatum* were survived even after 24 h of orally administration. In addition, no mortality or behavioural changes were observed. The rats were fed and allowed moving ordinarily. Thus, it has been found that LD50 of *T. nudatum* extract was not toxic even at doses around 5,000 mg/kg body weight.

3.3. Effects of *T. nudatum* ethanol extract on fasting blood glucose levels in alloxan-induced diabetic rats

In alloxan-induced diabetic rats (diabetic control, group B) a noticeable rise in fasting blood glucose level was noted in comparison with the (normal control, group A). Glibenclamide encourages a substantial decrease ($P \leq 0.001$) in the levels of blood glucose when it had been applied in treating alloxan-induced diabetic rats in (group C). It was observed that the ethanol extract of *T. nudatum* showed a time-dependent hypoglycemic activity which was significant in medium dose (200 mg/kg body weight, $P \leq 0.01$) and high dose (400 mg/kg body weight, $P \leq 0.001$) (groups E and F). This was clearly noted after the treatment period of day 21 when compared with diabetic control group of rats (group B). For diabetic induced rats getting a dose of 100 mg/kg body weight *T. nudatum* extract (group D) the reduction of blood glucose levels was observed to be insignificant throughout the entire period of the treatment (Table 1). This reduction in blood glucose levels observed in rats treated with *T. nudatum* (in groups E and F)

exhibited similar time-dependent trend of significance when compared with rats treated with Glibenclamide (group C). Reactions to treatment in all the groups seemed to reach equilibrium at 14 days, since glucose levels did not show significant changes between day 14 and 21. However, there was no significant difference between the mean sugar levels of the normal and Glibenclamide - treated group.

3.4. Antidiabetic effect of *T. nudatum* ethanol extract on body weight of diabetic rat

Throughout the housing period, the body weight of normal control group was found to be stable as shown in table 2. A high reduction in rat's body weight was noticed during Alloxan treatment particularly after 21 days. The reduction in Alloxan-mediated body weight was reversed by *T. nudatum* ethanol extract in a dose-dependent manner specifically when rats were treated with high and medium doses (400 mg/kg and 200 mg/kg body weight) of *T. nudatum* ($P \leq 0.001$ for both treatment doses). This body weight value correction was also determined to be more distinct only after 10 days in a comparable fashion as in Glibenclamide treatment ($P \leq 0.00$) and when paralleled with alloxan-induced diabetic rats.

3.5. Effects of *T. nudatum* ethanol extract on hematological parameters of diabetic rats

There were no noteworthy contrasts in the hematological constituents of blood parameters between, 400 mg/kg, 200 mg/kg and 100 mg/kg of *T. nudatum* treated group and diabetic control group.

2.6. Effects of *T. nudatum* ethanol extract on biochemical parameters of diabetic rats

The outcomes in Table 3 demonstrated that serum creatinine, serum cholesterol and serum urea levels were diminished significantly to just about normal levels with major increment in serum protein level following 10 days in diabetic rats treated with high and medium measurements (400 and 200 mg/kg body weight) of *T. nudatum* ethanol extricate after alloxan treatment ($P \leq 0.01$ and , $P \leq 0.001$). The adjustments of these parameters were seen to be more significant after treatment with high dose (400 mg/kg) of *T. nudatum* extract ($P \leq 0.001$) in a comparative pattern when Glibenclamide treatment is used ($P \leq 0.001$). It was noticed that treatment of *T. nudatum* ethanol extract at low dose of (100 mg/kg body weight) neglected to turn around the adjusted biochemical parameters in rats induced by alloxan. The other biochemical parameters were not displaying modification in values for

various groups when compared with diabetic control group. The concentrations of AST, ALT, and ALP followed the same pattern in all groups. Generally, treated group demonstrated similar but slightly lower enzyme levels than the Glibenclamide treated diabetic group. AST concentration was highest in the untreated diabetic rat group, and lowest in the normal non-diabetic group. Treatment of diabetic rats with Glibenclamide, extract of *T. nudatum* reduced the concentrations of AST to comparatively near-normal values. The results of Serum Alanine aminotransferase concentrations showed the same pattern as AST. Mean ALT concentrations were highest in the untreated diabetic control group almost double the concentration of the normal non-diabetic group, but reduced to near normal by Glibenclamide, and almost to Glibenclamide level by *T. nudatum* extract. Serum alkaline phosphatase levels showed similar patterns as AST and ALT. The mean concentrations of this serum enzyme were very similar in the normal non-diabetic, Glibenclamide -treated diabetic and *T. nudatum* t extract treated diabetic groups.

Table -1: Effect of *T. nudatum* on fasting blood glucose level in Alloxan induced diabetic rats

Group	Treatment	Fasting blood glucose level (mg/dl)			
		Basal value	7th day	14th day	21th day
A	Normal Control	91.36± 3.83	93.74 ± 2.93	93.20 ± 1.74	90.2 ± 2.44
B	Diabetic Control	296.73 ±5.27	289.80 ±5.33	294.73 ±5.52	292.31 ±5.54
C	Diabetic + Glibenclamide (10 mg/kg)	288.68 ±5.35	207.17 ±6.92***	185.04 ±5.13***	179.86 ±5.24***
D	Diabetic + Ethanolic extract (125 mg/kg)	294.68 ± 4.75	280.53± 5.06	268.86 ± 6.54	257.91 ± 4.50
E	Diabetic + Ethanolic extract (250 mg/kg)	287.24 ± 4.34	260.81 ± 5.37*	258.37 ± 6.65**	254.58 ± 6.44**
F	Diabetic + Ethanolic extract (5000 mg/kg)	290.39 ± 4.41	214.75 ±4.71***	200.38 ± 3.79***	191.6 ± 3.52***

Values are: Mean ± S.E.M; n=6

*** Significant at (P < 0.05) as compared to Diabetic Control**

Table -2: Effect of *T. nudatum ethanol* extract on body weight in alloxan induced diabetic rats.

Group	Treatment	Body weight of the animal (g)			
		Initial	7th day	14th day	21th day
A	Normal Control	256.78 ± 2.39	258.13 ± 2.41	260.78 ± 2.84	265.525 ± 2.12
B	Diabetic Control	258.64 ± 3.01	176.35 ± 2.75	161.55 ± 2.72	148.66 ± 1.18
C	Diabetic + Glibenclamide (10 mg/kg)	261.64 ± 2.55	258.13 ± 2.24*	251.46 ± 2.16*	246.85 ± 1.52*
D	Diabetic + Ethanolic extract (250 mg/kg)	261.21 ± 2.36	232.58 ± 2.54	217.12 ± 2.59	205.84 ± 1.12
E	Diabetic + Ethanolic extract (500 mg/kg)	260.69 ± 2.85	254.02 ± 2.51*	246.43 ±1.78*	237.11 ± 1.57*

F	**Diabetic + Ethanolic extract (1000 mg/kg)**	**261.72 ± 2.64**	**255.00 ± 2.53***	**248.90 ± 2.14***	**241.82 ± 1.36***

Values are: Mean ± S.E.M; n=6

***Significant at (P < 0.05) as compared to Diabetic Control.**

Table-3: Biochemical parameters of alloxan induced diabetic rats after given *T. nudatum ethanol* extract for 10 days

Group	Treatment	Serum Urea (mg / dl)	Serum Creatinin (mg/dl)	Serum Cholesterol (mg/dl)	Serum Protein (mg/dl)
A	**Normal Control**	**29.13 ± 1.07**	**0.54 ± 0.70**	**101.96 ± 1.97**	**6.20 ± 0.28**
B	**Diabetic Control**	**61.03 ± 1.09**	**1.44 ±0.08**	**186.48 ±1.36**	**5.42 ± 0.89**
C	**Diabetic + Glibenclamide (10 mg/kg)**	**32.59 ± 1.26 *****	**0.63 ±.03*****	**113.7 ±2.12*****	**6.10 ±0.21*****
D	**Diabetic + Ethanolic extract (250 mg/kg)**	**58.07 ± 1.47**	**1.24 ± 0.05**	**176.46 ± 5.41**	**5.07 ± 0.16**
E	**Diabetic + Ethanolic extract (500 mg/kg)**	**41.91 ± 1.64*****	**0.84 ± 0.05*****	**132.57 ± 2.95*****	**5.72 ± 0.22****
F	**Diabetic + Ethanolic extract (1000 mg/kg)**	**35.78 ± 0.63*****	**0. 69 ± 0.06*****	**117.86 ± 2.48*****	**5.99 ± 0.27*****

Values are Mean ± S.E.M; n=6,

***Significant at (P < 0.05) as compared Diabetic Control**

4. DISCUSSION AND CONCLUSION:

The major mechanism underlying hyperglycemia comprises more hepatic glycogenolysis and gluconeogenesis (over-production) and reduced usage of glucose by the tissues [16].

The present study results showed that *T. nudatum* extract (400 and 200 mg/kg b.w.) decreased the level of glucose in alloxan induced diabetic animals and in glucose loaded animals. It has been shown that Alloxan can cause tissue injury and induce free radical production [17]. The pancreas is mainly vulnerable to the activity of alloxan-induced free-radical damage. In addition, the loss of tissue proteins and the increase on the muscle wasting can be as a result of induction of diabetes with alloxan which generally indicated by the loss of body weight [18].

Our study experimentally confirmed that T. nudatum exhibited hypoglycemic activity to treat alloxan induced diabetic rats. A significant decrease in the blood glucose level was observed in the diabetic rats administered with *T. nudatum* extract in comparison with diabetic control rats as in Table 1.

In this study, a significant reduction in blood glucose level was reached by using different doses of ethanolic extraction of *T. nudatum*. For instance, a little or no significant reduction was found using 250 mg/kg extract dose of *T. nudatum,* while 400 mg/kg and 200 mg/kg doses revealed a higher reduction in the blood glucose level ($P \leq 0.001$). The extract of *T. nudatum* such as Glibenclamide can induce hypoglycemia by releasing insulin and stimulating its action, thus improving the uptake of cell and the glucose utilization in

rats. The extracts of plant might as well comprise biomolecules which may enhance the sensitization of the receptor of insulin to insulin or stimulate the β- cells of pancreatic islets to secret insulin that might guide to improvement of enzymes responsible for carbohydrate metabolizing in the way of the rearrangement of normal blood glucose level. It is likely that *T. nudatum* extracts might perform by indefinite ways to stimulate the production of insulin from the pancreatic islets of Langerhans besides.

It can be obvious that the extracts of *T. nudatum* had altered the body weight of diabetic rats (Table 2 2). In general, there was a drop in the body weight of the normal control (i.e., diabetic untreated group) as a result of glucose consumption and shift to catabolism of protein and fats, although the intake of food is less in normal control group than in diabetic rat groups [19]. The final weight of normal control (untreated control group) was higher than at the start of the experiment. In contrast, there was a reduction in the body weight of diabetic control group. Likewise, the groups treated with *T. nudatum* and Glibenclamide extracts stopped the decline in the body weight significantly, which might be attributable to its shielding property in monitoring muscle wasting, i.e., gluconeogenesis reversal and might also be attributable to appropriate control of glycemic. Correction of the loss of body weight might be caused by the consumption of a source of energy such as glucose in place of proteins and fats secondary to increased serum insulin [19]. The metabolic pathway shift to other source of energy (carbohydrate) with preserving fats and proteins in addition to their increased biosynthesis resulted in prevention of body weight decrease in treated diabetic rats with *T. nudatum* [20].

WBC and RBC counts, haematocrit, hemoglobin and RBC indices in treated diabetic rats with T. nudatum had not changed significantly and stayed within normal limits.

In diabetic rats after the administration of *T. nudatum* (Table 3), the levels of total cholesterol have been decreased significantly. This effect may be due to low level of lipolysis and or low activity of cholesterol biosynthesis enzymes which are under the insulin control. As insulin has a potent inhibitory effect on lipolysis in adipocytes, insulin lack is correlated with excess lipolysis and increased influx of free fatty acids to the liver [21,22].

High serum metabolic enzyme levels are indicators of compromised liver functions due to oxidative stress in diabetic rats. Serum levels of metabolic enzymes (AST, ALT,ALP) were drastically reduced to near

normal levels by Leaf +seed extracts these reversal of diabetes induced tissue damage process were confirmed by the photomicrographs of liver and kidney tissues of leaf , as well as leaf+ seed-treated rats, compared to the untreated diabetic control group. The photomicrographs also revealed that seed extract only partially ameliorated tissue damage, while leaf +seed extract appeared to have completely restore the tissue to normal state.

In uncontrolled diabetes the diabetic nephropathy is severe micro-vascular complication leading to glycosylation of renal basement membranes and result in increased creatinine concentrations [23]. Phytochemical studies of ethanolic extract showed the existence of flavonoid and phenolic compounds. The observed effects could have been induced by any of flavonoid compounds. Nevertheless, it has been reported that flavonoids constitute active biological principles of most medicinal plants with antidiabetic and hypoglycemic properties [24]. Therefore, this active principle might be responsible for the observed antidiabetic effect of the *T. nudatum* extract.

In conclusion, this study has revealed that ethanolic extracts of T. nudatum have great anti-hyperglycaemic potentials explorable for the treatment of diabetes-related pathogenesis, which appears to be more effective than the standard drug Glibenclamide, but which has the advantage of eliminating the side-effects of the latter, since it is routinely consumed as food. Additional pharmacological investigations are required to elucidate the mechanism of the observed antihyperglycemic effect.

Disclosure of conflict of interest

None.

Funding:

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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