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Anti-diabetic property of ethanolic extract of *Andrographis paniculata* in streptozotocin-diabetic rats

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KEY WORDS *Andrographis paniculata*; diabetes mellitus; glucose tolerance test; insulin; leptin; triglycerides; cholesterol; glucose-6-phosphatase; glycogen

ABSTRACT

AIM: To investigate the anti-diabetic effect of a crude ethanolic extract of *Andrographis paniculata* in normal and streptozotocin (STZ)-induced diabetic rats. **METHODS & RESULTS**: Oral administration of the extract at different doses (0.1, 0.2, and 0.4 g/body weight) significantly reduced the fasting serum glucose level in STZ-diabetic rats compared to the vehicle (distilled water), but not in normal rats. This effect was dose-dependent. A similar result was seen with metformin (0.5 g/body weight). In the glucose tolerance test, an oral administration of the extract at the same doses suppressed the elevated glucose level in normal and diabetic rats, as did metformin. The effects were also dose-respondent. In the long-term experiment, the extract (0.4 g/body weight), metformin (0.5 g/body weight), and vehicle were given twice daily to diabetic rats for 14 d. On d 15, fasting serum glucose levels were found to be significantly lower in the extract- and metformin-treated groups ($P < 0.001$) than in the vehicle-treated group. The mean food and water intakes over 14 days were significantly lower in the extract-treated group ($P < 0.05$, $P < 0.01$, respectively) and also in the metformin-treated group (both $P < 0.001$) when compared to the vehicle-treated group. No significant change in insulin level was observed among the 3 groups of diabetic rats. The extract, like metformin, maintained the leptin levels after 14-d treatment, whereas this level was significantly decreased ($P < 0.05$) in the vehicle-treated group. The activity of hepatic glucose-6-phosphatase (G-6-Pase) was significantly reduced by the extract as well as by metformin (both $P < 0.05$). No significant difference in hepatic glycogen stores was noted among the 3 groups. The extract caused 49.8 % reduction of fasting serum triglyceride levels, compared to 27.7 % with metformin. However, neither the extract nor metformin significantly affected serum cholesterol level. **CONCLUSION**: The ethanolic extract of *A paniculata* possesses antidiabetic property. Its antidiabetic effect may be attributed at least in part to increased glucose metabolism. Its hypotriglyceridemic effect is also beneficial in the diabetic state.

INTRODUCTION

Diabetes mellitus is a metabolic disorder characterized by hyperglycemia, altered metabolism of lipids, carbohydrates, and proteins, and an increased risk of complications from vascular disease[1]. In spite of the introduction of hypoglycemic agents, diabetes and its related complications continue to be a major medical problem. Like many other diseases, diabetes has been treated by oral administration of plant extracts based on traditional practice since ancient times[2]. More than 400 local plant treatments for diabetes mellitus have been recommended by the traditional health care provider[3,4]. However, only a few of the traditional plant treatments for diabetes have received scientific scrutiny, and the World Health Organization has recommended that this area warrants attention[5].

Andrographis paniculata (Burm f) Nee (*Acanthaceae*) is a bitter shrub that is widely used as traditional medicine in Southeast Asia. It is claimed to possess many antibacterial, anti-inflammatory, immunological, antivenin[6], antihepatotoxic[7] and hypotensive[8] properties. In Malaysia, this plant is considered as a potent medicine for the treatment of diabetes and hypertension[9]. However, a review of the current literature

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indicates that the only report on the hypoglycemic effect of *A paniculata*, was by Borhanuddin M and his colleagues[10] who found that an aqueous extract of this plant could improve glucose tolerance in normal rabbits.

Streptozotocin (STZ) is widely used to induce experimental diabetes, as it is less toxic than other chemical agents which induce diabetes[11]. Rats treated with STZ display many of the features seen in human subjects with uncontrolled diabetes and provide valuable information about the pathophysiological changes that lead to chronic diabetic complications[12,13].

In the present study, we evaluated the antidiabetic effect of an ethanolic extract of *A paniculata* on fasting blood glucose and glucose tolerance in normal and STZ-induced Sprague-Dawley (SD) diabetic rats, and compared its effects with those of metformin, a biguanide used as an antidiabetic agent. We also investigated whether the extract could affect some biochemical markers of carbohydrate metabolism, such as insulin, leptin content, liver glycogen and glucose-6-phosphatase (G-6-Pase) activity, as well as lipids, such as triglyceride (TG) and total cholesterol (TC) in STZ-diabetic rats.

MATERIALS AND METHODS

Preparation of the extract The fresh aerial parts of *A paniculata* were purchased from the local market and identified as *A paniculata* (Burm. f.) Nees (*Acanthaceae*) by Professor Wee Yeow Chin, Department of Botany, National University of Singapore. A dried specimen is deposited in the herbarium (vouch No 569).

The fresh aerial parts of *A paniculata* (1 kg) were blended and extracted with 80 % ethanol exhaustively at room temperature. After filtration with cotton wool, the filtrate was centrifuged at 10 000 × *g* for 20 min. The supernatant was concentrated at 40 ℃ by a rotavapor (Buchi Labortechnik AG. Switzerland), and approximately 0.5 L of an aqueous solution was obtained. This solution was then freeze-dried to yield 70 g of the green powder. The powder was suspended in distilled water before use.

Animals Locally bred male SD rats, 200 – 250 g, were obtained from the Laboratory Animal Center, National University of Singapore and housed in a room with controlled temperature (22 ℃ ± 2 ℃) on a 12:12 light/dark cycle (lights on at 06:00 AM). For the 2-wk study, rats were housed 5 in a cage or were kept individually in metabolic cages for 3 d before and until the end of the experiment. Unless otherwise indicated, animals had free access to pelleted food (Glen Forrest, WA, Australia) with tap water *ad libitum*.

Experimental induction of diabetes in rats Diabetes was induced in rats that had been fasted for 18 h by intraperitoneal injection of 60 mg/kg body weight (bw) of STZ (Sigma Chemical Co, MO, USA), freshly dissolved in citrate buffer (0.01 mol/L, pH 4.5) to give a concentration of 30 g/L. The diabetic state was assessed by measuring non-fasting serum glucose concentration 48 h after STZ treatment. The rats with a serum glucose level above 3000 mg/L, as well as with polydipsia, polyuria and polyphagia were selected for the experiment.

Collection of blood sample Blood samples were collected in tubes by tail clipping, and centrifuged at 1000 × *g* for 15 min to obtain the serum.

Experimental procedure

1 Effects on fasting glucose levels of normal and diabetic rats The extracts at graded doses (0.1, 0.2, and 0.4 g/kg) were given orally to different groups (each $n = 6$) of normal and diabetic rats after drawing the first blood samples. Additional samples of blood were collected at 1, 2, and 3 h after administration of the extracts. A reference drug, metformin (0.5 g/kg) (Pharmacy, National University Hospital, Singapore), was given to another group of rats, while control animals received the vehicle (distilled water). Blood samples were drawn from these groups of rats at identical times.

2 OGT test in normal rats Prior to an OGT test, rats were fasted for 12 – 15 h. Distilled water, the reference drug, metformin (0.5 g/kg), or different doses (0.1, 0.2, or 0.4 g/kg) of the ethanolic extract of *A paniculata* were orally administered to groups of 6 rats. Thirty minutes later, glucose (3 g/kg) was orally administered to the rats in each group. Blood samples were taken from the tail vein at −30 min (just before the distilled water, metformin or the extract administration), 0 min (just before the glucose load), 60, 120, and 180 min (after the glucose load) for the assay of glucose.

3 OGT test in the diabetic rats Four days after the STZ administration, the OGT test was performed in the diabetic rats as described above, with similar controls and doses of the extract.

4 Oral administration of the ethanolic extract of *A paniculata* in diabetic rats for 14 d Four days after the STZ administration, 18 diabetic rats were randomly divided into 3 groups of 6 rats each and were treated orally twice daily (at 09:00 AM and 06:00 PM) for 14 d as

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follows: Group 1, distilled water; Group 2, 0.4 g/kg extract; Group 3, 0.5 g/kg metformin.

Before the start of the experiment, blood was collected to measure the fasting serum glucose, insulin, leptin, triglyceride (TG), and total cholesterol (TC) levels. Food and water were given ad libitum; the amount consumed as well as the body weight were recorded daily. On the evening of day 14, all rats were fasted overnight and killed by decapitation the following morning. Blood was collected by drainage from the carotids and kept on ice for the above measurement. The livers were removed and immediately frozen in liquid nitrogen and stored at −70 ℃ for various assays.

Determination of glucose, TG, TC, insulin, and leptin concentrations in serum Glucose concentrations were measured by the glucose oxidase method[14], using the glucose analyzer (Sigma Chemical Co, MO, USA). TC and TG concentrations were measured by the colorimetric method, using wet reagent diagnostic kits (Boehringer Mannheim GmbH). Serum insulin was estimated by enzyme-linked immunosorbent assay (ELISA) using a kit purchased from Mercodia, Uppsala, Sweden. Serum leptin level was also measured by ELISA using a kit from R&D systems, MN, USA.

Liver glycogen and glucose-6-phosphatase (G-6-Pase) assay Liver glycogen content was measured according to the method of Murat and Serfaty[15]. Weighed frozen tissue was placed in chilled citrate buffer (0.1 mol/L, pH 4.5) and homogenized with polytron homogenizer (Kinematica, GmbH, Switzerland). After measuring the free glucose in the homogenate, amyloglucosidase (Sigma Chemical Co, MO, USA) was added to the homogenate at a concentration of 1 g enzyme/L of homogenate and incubated overnight (16 h) at room temperature. The glycogen content of the liver samples was estimated by comparing glucose liberated from the tissue with a standard curve obtained by treating known amounts of glycogen with amyloglucosidase enzyme.

G-6-Pase activity was assayed according to Baginsky, *et al*[16] by estimation of inorganic phosphate liberated from glucose-6-phosphate (G-6-P). For this assay, 1 g of frozen liver tissue was homogenized in ice-cold sucrose solution with a Polytron homogenizer. The homogenate was centrifuged sequentially at 11 000 × *g* for 30 min, then at 105 000 × *g* for 1 h using an ultracentrifuge (Beckman L8−70). The solid pellet was resuspended in ice-cold sucrose/edetic acid solution and used as the source of the enzyme. Tubes were divided into samples, blanks and standard. To each were added 0.1 mL of sucrose/EDTA buffer (0.25 mol/L/1 mmol/L, pH 7.0), 0.1 mL of G-6-P (100 mmol/L), and cacolyte buffer solution. This was followed by the addition of 0.1 mL of sample to the sample tube, 0.1 mL of sucrose/EDTA solution to the blank and 0.1 mL of different concentrations of K_2HPO_4 (0.5 mmol/L, 1 mmol/L, 1.5 mmol/L, and 2 mmol/L) to the standard tube. All tubes were incubated at 37 ℃ for 15 min and the enzyme activity was terminated by adding 2 mL TCA/ascorbate (10 %/2 %). The tubes were then centrifuged at 3000 × *g* for 10 min. To 1.0 mL of this clean supernatant were added 0.5 mL ammonium molybdate (1 %) and 1 mL of Na-arsenite/Na-citrate (2 %/2 %). The tubes were then allowed to stand for 15 min at room temperature and absorbance was read at 840 nm. Amount of inorganic phosphate liberated by the enzyme was calculated by comparing the absorbance values of the standard. The protein content in the sample was determined by the Bio Rad Protein Assay Reagent (Bio-Rad Laboratories, CA, USA). Enzyme activity was expressed in (μmol of Pi liberated/min per mg protein.

Statistical analysis The results are expressed as $\bar{x} \pm s_{\bar{x}}$. The significance of the differences in the values of food and water intakes between the different groups of diabetic rats over the 14-day period was analyzed by two-way analysis of variance (ANOVA). Other statistical analysis was performed by one-way ANOVA followed by the Tukey test. P values <0.05 were considered to be significantly different.

RESULT

Acute effect of the extract of *A paniculata* in normal and diabetic rats

Hypoglycemic test in normal and STZ-diabetic rats In normal rats, the ethanolic extract of *A paniculata* at all 3 doses did not produce a significant decrease in glucose levels within 3 h after oral administration. Neither did metformin. In diabetic rats, however, the serum glucose levels were significantly decreased in the extract-treated group compared to the vehicle at 60 min and 120 min. This antidiabetic effect was dose-dependent. The extract at 0.4 g/kg reached a maximum reduction of 17.7 % at 120 min. These levels also were markedly decreased in the metformin-treated group during 3 h after oral administration, with a maximum reduction of 33.6 % at 180 min (Fig 1).

Oral glucose tolerance test in normal and diabetic

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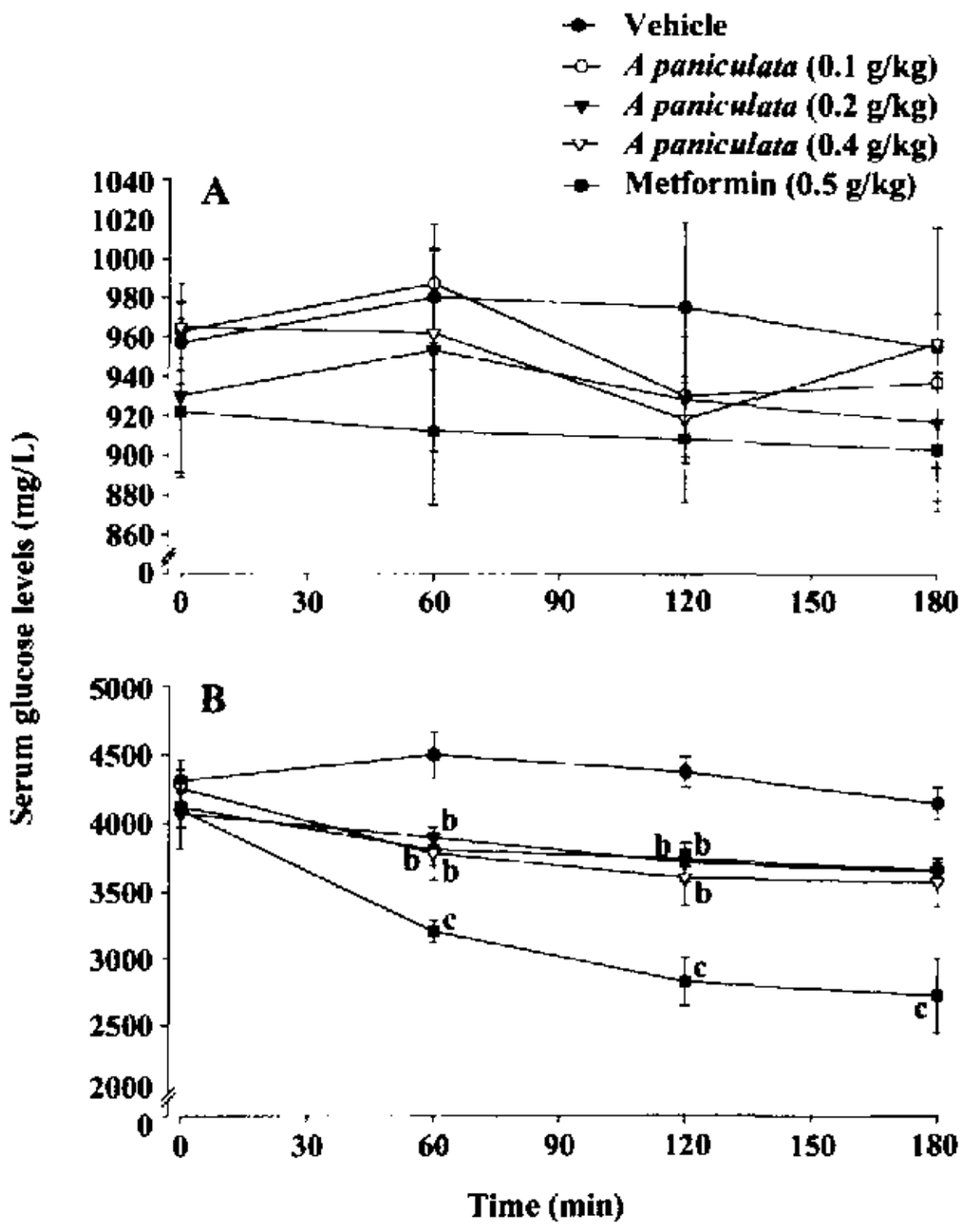

Fig 1. Effects of ethanolic extract of *A paniculata* on mean fasting serum glucose levels in normal (A) and STZ-induced diabetic (B) rats. $n = 6$ rats. $\bar{x} \pm s_{\bar{x}}$. $^bP < 0.05$, $^cP < 0.001$, compared to the corresponding vehicle group (one way ANOVA followed by Tukey test).

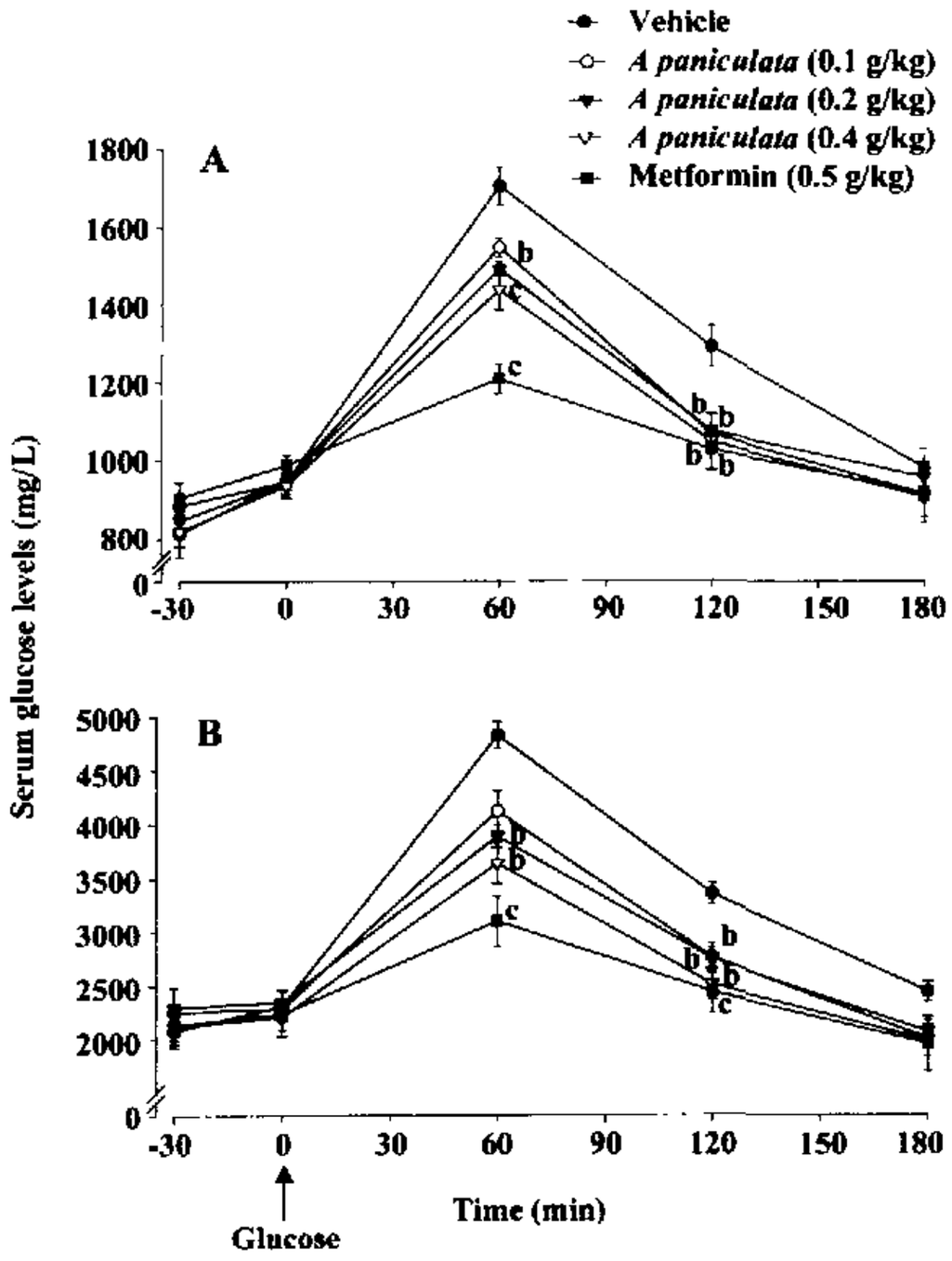

Fig 2. Effects of ethanolic extract of *A paniculata* (0.4 g/kg) and metformin (0.5 g/kg) on glucose tolerance in normal (A) and STZ-induced diabetic (B) rats. $n = 6$ rats. $\bar{x} \pm s_{\bar{x}}$. $^bP < 0.05$, $^cP < 0.001$ compared to the corresponding vehicle group (one way ANOVA followed by Tukey test).

rats After the normal and diabetic rats were challenged with an oral glucose load, serum glucose levels reached a peak at 60 min, and gradually decreased to pre-glucose load level. In both normal and diabetic groups, the extract at 0.2 and 0.4 g/kg significantly suppressed the elevated serum glucose at 60 min and 120 min after glucose load as compared to vehicle-treated rats. At 0.1 g/kg, the extract significantly decreased glucose level only at 120 min. Metformin 0.5 g/kg also depressed the elevated serum glucose level 60 min and 120 min after glucose load in both normal and diabetic groups (Fig 2).

Repeated administration of the *A paniculata* ethanolic extract in diabetic rats

Food and water intake At the start of the experiment (on d 0), food and water intake was similar in all groups of diabetic rats. However, the mean food and water intake over the 14-d treatment in the extract-treated group (17.2 g/100 g bw, 72.6 mL/100 g bw, respectively) was significantly lower when compared to those in the vehicle-treated rats (18.4 g/100 g bw and 80.4 mL/100 g, respectively). These values were also markedly decreased in the metformin-treated diabetic rats (14.7 g/100 g bw and 52.5 mL/100 g bw, respectively) (Fig 3, 4)

Fasting serum glucose, insulin, leptin, TG and TC levels The fasting serum glucose levels in the extract- as well as metformin-treated diabetic rats were significantly lower than in the vehicle-treated diabetic rats after 14-d treatment. However, no significant change was found in the insulin levels among the three diabetic groups. The extract and metformin could maintain the leptin level of diabetic rats during 14-d treatment, whereas this level was markedly decreased in the vehicle-treated diabetic rats (Tab 1).

The oral administration of the extract for 14 d significantly reduced serum TG level by 49.8 %. Metformin also caused a 27.7 % decrease in serum TG level. Serum TC was increased by 1 % and 6 %, respectively in the extract and metformin-treated diabetic group,

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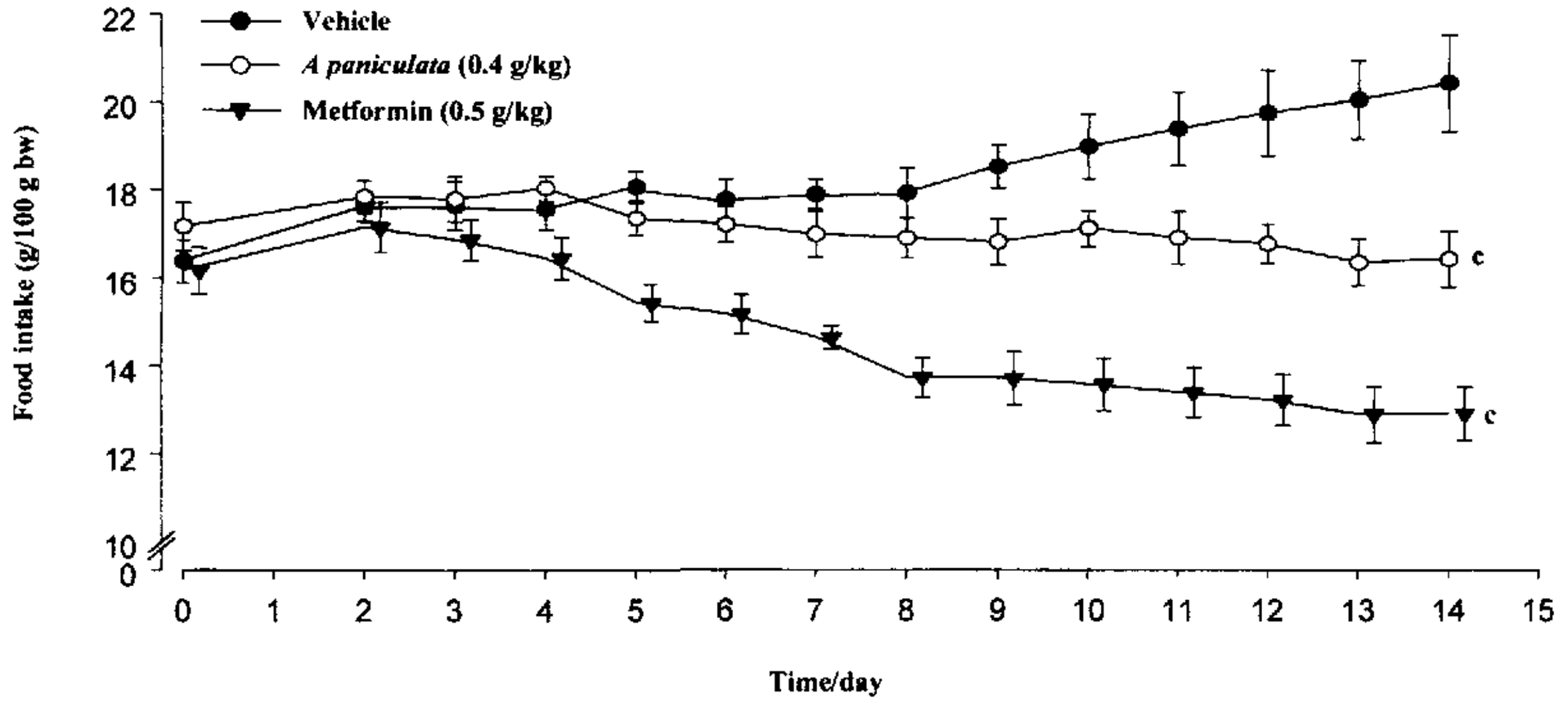

Fig 3. Changes in mean food intake (g/100 g bw) of diabetic rats treated with *A paniculata* (0.4 g/kg), metformin (0.5 g/kg), and vehicle over 14 d. $n = 6$ rats. $\bar{x} \pm s_{\bar{x}}$. Values in the extract- and metformin-treated group are significantly lower than in the corresponding vehicle-treated group ($F_{1140} = 36.19$, $P < 0.001$; $F_{1140} = 282.14$, $P < 0.001$; respectively, two-way ANOVA).

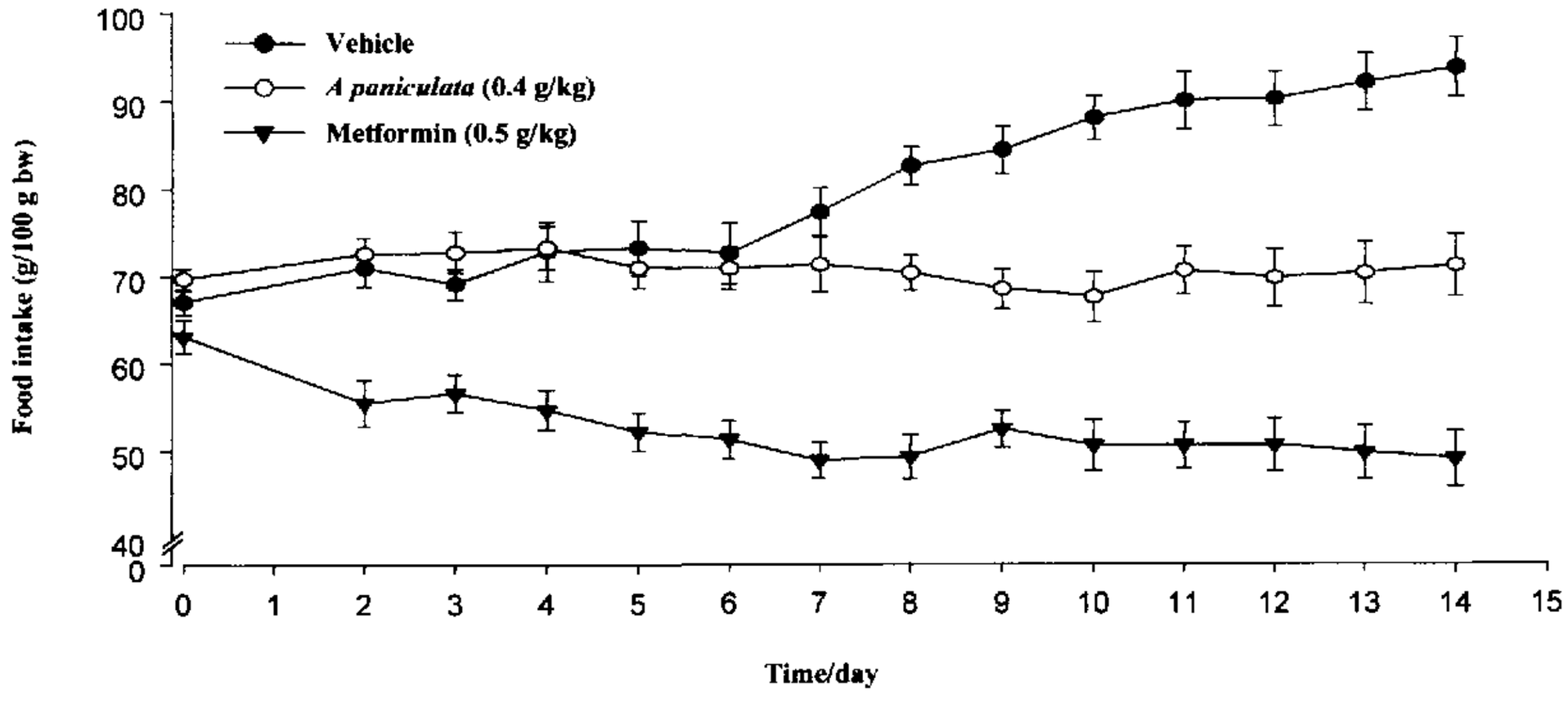

Fig 4. Changes in mean water intake (mL/100 g bw) of diabetic rats treated with *A paniculata* (0.4 g/kg), metformin (0.5 g/kg), and vehicle over 14 d. $n = 6$ rats. $\bar{x} \pm s_{\bar{x}}$. Values in the extract- and metformin-treated group are significantly lower than in the corresponding vehicle-treated group ($F_{1140} = 82.20$, $P < 0.001$; $F_{1140} = 757.77$, $P < 0.001$, respectively, two-way ANOVA).

whereas it was increased by 22 % in the vehicle-treated diabetic rats. The differences were not significantly different (Tab 1).

Live glycogen content and G-6-pase activity

The extract as well as metformin tended to cause an increase in the liver glycogen content of diabetic rats; no statistical significance was found between these groups. Hepatic G-6-Pase activities were significantly decreased in diabetic rats (both $P < 0.05$) treated with the extract and metformin as compared to the vehicle (Tab 2).

DISCUSSION

The present study revealed that oral administration of three different single doses of the ethanolic extract of *A paniculata* could improve glucose tolerance in normal and

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Tab 1. Mean serum glucose, insulin, leptin, cholesterol, and triglyceride levels in the STZ-diabetic rats treated with *A paniculata* for 14 d. $n = 6$ rats. $\bar{x} \pm s_{\bar{x}}$. $^bP < 0.05$, $^cP < 0.01$ *vs* vehicle. $^eP < 0.05$ *vs* Day 0. (One-way ANOVA followed by Tukey test).

Parameter	Day	Vehicle	Metformin	*A paniculata*
Glucose (mg/L)	0	3900 ± 272	3728 ± 311	3912 ± 296
	15	4962 ± 208^c	3385 ± 188^c	3430 ± 148^c
Insulin (μg/L)	0	575 ± 46	645 ± 99	532 ± 72
	15	522 ± 83	668 ± 95	611 ± 87
Leptin (ng/L)	0	99.4 ± 8.5	101.7 ± 10.3	100.2 ± 11.2
	15	72.0 ± 5.6^e	96.6 ± 6.6^b	94.1 ± 5.2^b
Triglyceride (mg/L)	0	1426 ± 167	1389 ± 104	1335 ± 206
	15	1471 ± 80	1004 ± 42^b	670 ± 89^c
Cholesterol (mg/L)	0	706 ± 80	692 ± 46	820 ± 53
	15	864 ± 47	735 ± 48	829 ± 79

STZ-induced diabetic rats. In the OGT curve, the peak reflects the extent of intestinal glucose absorption and hepatic metabolism. The finding that metformin could suppress the peak of these curves by 29.0 % and 25.2 % in normal and diabetic rats respectively suggests that metformin could decrease glucose absorption in the intestine and increase glucose metabolism in the liver. This is consistent with previous reports[17,18]. The extract at a dose of 0.4 g/kg suppressed the peak of the OGT curves in normal and diabetic groups by 15.7 % and 17.3 %, respectively. Our results thus indicate that the effect of the extract on glucose absorption and hepatic metabolism was weaker than that of metformin.

A single dose of metformin could markedly reduce the serum glucose level but in diabetic rats only. Like the extract, it did not affect insulin level in diabetic rats even after 14 days of treatment. This is in accordance with the reports which demonstrated that metformin does not produce hypoglycemia in the non-diabetic state[19,20]. Metformin has been shown to act by inhibiting hepatic glucose production[21,22] and increasing the sensitivity of peripheral tissues to insulin[23,24]. Metformin is thus more aptly described as an antihyperglycemic rather than hypoglycemic agent[25]. In our study, a single dose of the extract significantly decreased the basal glucose level in the STZ-diabetic group, but not in normal rats. A 14-d administration of the extract at a dose of 0.4 g/kg attenuated the fasting glucose level compared to the vehicle, but did not affect serum insulin concentration. Thus like metformin, the extract does not appear to act by stimulating insulin from the pancreas.

The extract and metformin could decrease food and water intake of the diabetic animals during the 14-d treatment. They also prevented serum leptin levels in the diabetic rats from decreasing. Leptin, the ob gene product, is a 16-kD protein secreted primarily by adipocytes[26]. Many recent studies have demonstrated that circulating leptin levels decreased markedly and rapidly after the induction of STZ type I diabetes in rats[27-29]. This leptin deficiency contributes to the onset of diabetic hyperphagia while restoration of normal physiological circulating leptin concentration prevents the onset of the hyperphagic response[27]. It has been proposed that reduction of circulating leptin in uncontrolled type I diabetes may be a consequence of decreased adipocyte glucose uptake and metabolism[29]. Insulin increases leptin levels in this kind of diabetic rats as it promotes glucose uptake and metabolism by adipose tissue[29]. It is suggested that the extract and metformin could decrease food intake in diabetic rats by maintaining serum leptin levels. The effect of metformin in maintaining circulating leptin levels in STZ-diabetic rats may be attributed to the insulin-stimulated glucose uptake in adipocytes[30] and glucose oxidation by adipose tissue[18]. The potency of the extract was similar to that of metformin with regards to its effect on serum leptin levels. This leads to the hypothesis that *A paniculata* may have an effect on glucose uptake and metabolism by adipose tissue. Further experiments are required to confirm this.

Tab 2. Liver glycogen content and glucose-6-phosphatase (G-6-pase) activity in *A paniculata*-, metformin-, and vehicle-treated STZ-diabetic rats. $n = 6$ rats. $x \pm s_{\bar{x}}$. $^bP < 0.05$ *vs* vehicle (One-way ANOVA followed by Tukey test).

	Vehicle	Metformin (0.5 g/kg)	*A paniculata* (0.4 g/kg)
Liver glycogen (mg/g)	9.78 ± 0.89	14.63 ± 1.35	15.43 ± 2.01
G-6-Pase (mmol Pi/mg protein per min)	0.547 ± 0.029	0.435 ± 0.022^b	0.436 ± 0.034^b

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G-6-Pase has an important function glucose metabolism and homeotasis. It converts glucose-6-phosphate (G-6-P) *into glucose and phosphate and represents* 1) *the terminal* enzymatic step of hepatic and renal glucose production and 2) the common enzymatic step for both glucose-producing pathways, gluconeogenesis and glycogenolysis[31,32]. Previous studies have reported that G-6-Pase activity was increased in the STZ-induced type I diabetic rats; and that this is due to insulin deficiency[33-35]. Our result that metformin could decrease the G-6-Pase is in agreement with a previous study[36]. This value was also markedly decreased in the extract-treated diabetic rats. The finding indicated that the hypoglycemic effect of the extract may be mediated via suppressing the important enzymatic step in liver glucose production. Although no statistically significant difference was observed in the fasting glycogen content in the three diabetic groups, this content tended to be higher in the extract- and metformin-treated group compared to the vehicle-treated group. *A paniculata* has been reported in a previous study to be a hepatoprotective agent[7]. As the liver is a major organ involved in carbohydrate metabolism, a beneficial effect of the extract on liver function may contribute to its antihyperglycaemic property.

Hypertriglyceridemia and hypercholesterolemia are lipoprotein abnormalities that are characteristic of diabetes[1]. The adverse effect of raised TG and TC concentrations is that they increase the risk of coronary heart disease[37,38]. Our results show that the extract could reduce TG content by as much as 49.8 %, compared to 27.7 % by metformin. It also prevented the elevation of TC in diabetic rats. These effects of the extract on dyslipoproteinemia in STZ-diabetic rats are of potential clinical relevance.

Taken together, the present study reveals that the ethanolic extract of *A paniculata* possesses an antihyperglycemic property. It is unlikely that it acts as an insulin secretagogue and its main underlying mechanism remains to be elucidated, although it seems to be attributable to improved glucose metabolism. The extract could not normalize the fasting blood glucose in diabetic rats after 14-d treatment. Since the STZ-induced diabetic rats we used in the experiment resemble the insulin-dependent diabetes mellitus (IDDM) in human, insulin is necessary to treat this kind of diabetes. Oral antidiabetic drugs are suitable for non-insulin-dependent diabetes mellitus (NIDDM) patients at the early stage[39,40]. Typically, these NIDDM patients exhibit elevated circulating lipid concentrations and hypertension, which with hyperglycaemia, contribute to the microvascular lesions (retinopathy, glomerulopathy, peripheral neuropathy) commonly *observed in late stages of NIDDM. Given the value of* the extract in considerably lowering serum TG in STZ-diabetic rats and its anti-hypertensive property as reported by previous studies from our laboratory[8], we suggest that the extract is probably more efficient in NIDDM states.

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万方数据