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Kertas Asli/*Original Article*

Antihyperglycemic and Glucose Tolerance Activity of *Ficus deltoidea* Ethanolic Extract in Diabetic Rats

(Aktiviti Antihiperglisemik dan Toleransi Glukosa Ekstrak Etanol *Ficus deltoidea* dalam Tikus Diabetis)

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ABSTRACT

Ficus deltoidea or Mas cotek is one of the common medicinal plants used in Malaysia has been claimed to have antidiabetic activity. However, scientific evidence to confirm its efficacy is still lacking. Thus, the present study was undertaken to evaluate the potential of ethanolic extract of Ficus deltoidea to reduce hyperglycaemia in streptozotocin-induced diabetic rats at different prandial state. The results showed that, ethanolic extract of Ficus deltoidea significantly reduced fasting and postprandial hyperglycemia particularly after 4 and 6 hours of extract administration. Likewise, glucose tolerance activity was significantly improved in the presence of Ficus deltoidea ethanolic extract at a low dose, 100 mg/kg. It is suggested that ethanolic extract of Ficus deltoidea at particular doses, possess fasting and postprandial antihyperglycemic activity as well as glucose tolerance activity in streptozotocin-induced diabetic rats.

Keywords: Ficus deltoidea; diabetes; antihyperglycemic; postprandial; glucose tolerance

ABSTRAK

Ficus deltoidea atau Mas Cotek merupakan salah satu tumbuhan ubatan di Malaysia yang dikatakan mempunyai aktiviti antidiabetik. Walau bagaimanapun, bukti saintifik yang mengesahkan keberkesanannya masih kurang. Kajian ini bertujuan untuk menilai potensi ekstrak ethanol Ficus deltoidea sebagai agen hipoglisemia pada tikus diabetik aruhan streptozotocin. Keputusan menunjukkan bahawa ekstrak ethanol Ficus deltoidea secara signifikan mengurangkan hiperglisemia puasa dan pascaprandial terutama pada 4 dan 6 jam selepas pengambilan ekstrak. Begitu juga, aktiviti toleransi glukosa telah dipertingkatkan secara signifikan dengan kehadiran ekstrak ethanol Ficus deltoidea pada dos rendah, 100 mg/kg. Berdasarkan kajian ini, dicadangkan bahawa ekstrak ethanol Ficus deltoidea pada dos tertentu menunjukkan aktiviti antihiperglisemia puasa dan selepas prandial serta aktiviti toleransi glukosa pada tikus diabetik aruhan streptozotocin.

Kata kunci: Ficus deltoidea; diabetis; antihiperglisemia; pascaprandial; toleransi glukosa

INTRODUCTION

Diabetes mellitus remains as the major global health problems in most countries even though there are plenty of antidiabetic agents available in the market. This is due to side effects produced by some of these agents including hypoglycaemic coma, hepatorenal disturbances (Suba et al. 2004) and gastrointestinal adverse reaction (Campbell 2000) Therefore, searching for safer antidiabetic agents with less side effects should be continued. The uses of herbal remedies for diabetes treatment are well known since ancient times.

Ficus deltoidea from Moraceae family is one of the commonly used medicinal plants in Malaysia (Mat-Salleh & Latif 2002). Based on ethnobothanical approaches, this plant has been traditionally claimed to have antidiabetic property and has been used as traditional remedy for diabetes treatment. However, scientific evidence to confirm its efficacy is still lacking. Only two studies has been done which reported the glucose lowering effect of aqueous extract of *F. deltoidea* in normal rats (Aminudin et al. 2007) and mild diabetic rats (Adam et al. 2007). This plant which is native to Southeast Asia and Philiphines (Forest et al. 2003), also been used to treat other kinds of ailment such as headache and fever (Mat Salleh & Latif 2002). Recent studies reported on the antinociceptive activity (Sulaiman et al. 2008) and antiulcerogenic activity (Siti Fatimah Zahra et al. 2009) of aqueous extract of *F. deltoidea*. Hakiman and Maziah (2009) have found that aqueous extract of different *F. deltoidea* accessions possess non enzymatic and enzymatic antioxidant activities.

The present study was undertaken to evaluate the potential of ethanolic extract of *Ficus deltoidea* in reducing blood glucose level in streptozotocin-induced diabetic rats at different prandial states.

MATERIALS AND METHODS

CHEMICALS

Ethanol and diethylether were purchased from Merck, Germany. Carboxymethylcellulose (CMC), metformin, streptozotocin and glucose were purchased from Sigma Chemical Co. (St. Louise, USA).

PLANT MATERIAL AND EXTRACT PREPARATION

F. deltoidea plants were collected at Sungai Tengi Selatan, Selangor, Malaysia. The specimen was identified by taxonomist from Biodiversity Unit, Institute of Bioscience, Universiti Putra Malaysia. A specimen was deposited at the herbarium of the mentioned institute with voucher number SK1467/07. The leaves of *Ficus deltoidea* were dried at 45°C and ground into a fine powder. Ethanolic extract was prepared by soaking the sample powder into 70% ethanol for 3 days (100 g/L) at room temperature by changing solvent daily. The combined suspension was filtered through a whatman filter paper No. 54 and evaporated to dryness under reduced pressure.

EXPERIMENTAL ANIMALS AND DIABETES INDUCTION

Sprague Dawley rats used in the study were breed in house at Animal House of Malaysian Nuclear Agency. Adult male rats weighing 200-250 g were used in the study. Animals were housed in polycarbonate cages and fed on a standard laboratory pellet diet with water supplied *ad libitum*. All animal procedures were approved by Animal Care and Use Committee (ACUC), Faculty of Medicine and Health Science, Universiti Putra Malaysia (ACUC no: UPM/FPSK/PADS/BR/UUH/F01-00208). Diabetes was induced by a single intravenous (tail vein) injection of streptozotocin (60 mg/kg; 100 mg/ml in distilled water) under ether anesthesia. The solution of streptozotocin was freshly prepared, as the drug is very labile in solution. Fasting blood glucose was checked 7 days after injection and rats with blood glucose level more than 13.0 mmol/L were considered diabetic (Kesari et al. 2006). Diabetic rats were randomly divided into five groups (seven rats in each group). Group I (control rats) were given vehicle, 1% carboxymethylcelulose (CMC). Group II, III and IV were treated with ethanolic extract of *Ficus deltoidea* suspended in 1% CMC at doses of 100, 500 and 1000 mg/kg, respectively. Group V was treated with metformin at dose of 500 mg/kg.

ANTIHYPERGLYCEMIC TEST IN FASTING AND POSTPRANDIAL STATE

In fasting state, diabetic rats were fasted 12-hour prior to test whereas in postprandial state, diabetic rats were fasted 1-hour prior to test. After fasting period, rats were treated with *F. deltoidea* ethanolic extracts at different doses (groups II, III and IV) or metformin (group V) orally using intragastric gavage. Blood samples were collected before (0 hour) and after 2, 4 and 6 hour of extracts or metformin administration for the measurement of blood glucose concentration.

ORAL GLUCOSE TOLERANCE TEST (OGTT)

Fasting blood glucose was checked in 12 hours fasted diabetic rats (-30 min) followed by oral administration of *F. deltoidea* ethanolic extracts or metformin suspended in 1% CMC orally using intragastric gavage. Thirty minutes later (at 0 hour), rats of all groups were given glucose (1.5 g/kg; 100 mg/ml in distilled water) orally using intragastric gavage. Blood samples were collected just prior to glucose administration (0 min) and 30, 60, 120 and 180 minutes after glucose administration. Total glyceamic responses to OGTT were calculated from respective areas under the glucose curve ($AUC_{Glucose}$) at the 180 minutes observation period using a computer calculator software provided by Thomas Wolever from Department of Nutritional Sciences, University of Toronto, Toronto, Ontario, Canada (Jalil et al. 2008).

BLOOD COLLECTION AND DETERMINATION OF GLUCOSE LEVEL

Blood samples were collected from the tip of the rats' tails under mild ether anesthesia. The glucose level was determined using an electronic glucometer, Accu Check Advantage from Roche Diagnostic (Indianapolis, USA) (Jayakar & Suresh 2003).

STATISTICAL ANALYSES

All results are expressed as the mean ± standard deviation for a given number of observations. The data were analyzed using one way Analysis of Variance (ANOVA), followed by Tukey's post hoc test. The group means were considered significantly different at the level of $p < 0.05$.

RESULTS

ANTIHYPERGLYCEMIC ACTIVITY OF FICUS DELTOIDEA

Table 1 shows the effect of various doses of ethanolic extract of *F. deltoidea* on fasting blood glucose in streptozotocin-induced diabetic rats. It was shown that extract at doses of 100 and 500 mg/kg significantly reduced fasting blood glucose level after 2, 4 and 6 hours of administration whereas extract at dose of 1000 mg/kg significantly reduced fasting blood glucose after 4 and 6 hours of administration compared to the 0 hour. Metformin significantly reduced fasting blood glucose concentration after 2, 4 and 6 hours of administration.

The effects of various doses of ethanolic extract of *F. deltoidea* on postprandial blood glucose in streptozotocin-induced diabetic rats are shown in Table 2. Extract at dose of 100 mg/kg significantly reduced postprandial blood

TABLE 1. Effect of ethanol extract of *F. deltoidea* on fasting blood glucose level in streptozotocin-induced diabetic rats

Treatment group	Blood glucose level (mmol/L) (mean ± SD)			
	0 hr	2 hr	4 hr	6 hr
Control	17.97 ± 0.54	18.17 ± 1.17	16.80 ± 1.32	16.23 ± 1.12
F. deltoidea 100 mg/kg/b.w.	16.67 ± 1.44	14.00 ± 0.85 (16.02)**	12.93 ± 1.21 (22.44)***	12.69 ± 1.26 (23.88)***
F. deltoidea 500 mg/kg/b.w.	16.91 ± 1.32	12.94 ± 1.64 (23.48)***	11.96 ± 1.58 (29.27)***	11.96 ± 1.61 (29.27)***
F. deltoidea 1000 mg/kg/b.w.	17.90 ± 1.33	15.95 ± 1.61	14.02 c 1.66 (21.68)**	13.62 ± 2.66 (23.91)**
Metformin 500 mg/kg/b.w.	16.77 ± 0.72	8.14 ± 3.07 (51.44)**	3.19 ± 0.52 (81.00)***	3.60 ± 0.96 (78.53)***

Note: Values in bracket indicate percentage of blood glucose reduction relative to 0-hour of the respective treatment group. **p < 0.01 and ***p < 0.001 compared to 0 hour of the respective group

TABLE 2. Effect of ethanol extract of *F. deltoidea* on post prandial blood glucose level in streptozotocin-induced diabetic rats

Treatment group	Blood glucose level (mmol/L) (mean ± SD)			
	0 hr	2 hr	4 hr	6 hr
Control	26.60 ± 2.24	25.05 ± 3.64	22.88 ± 5.13	21.53 ± 3.33
F. deltoidea 100 mg/kg/b.w.	26.17 ± 3.56	22.49 ± 3.23	20.44 ± 3.09 (21.90)**	18.80 ± 2.12 (28.16)***
F. deltoidea 500 mg/kg/b.w.	23.8 1 ± 0.98	21.21 ± 2.48	21.29 ± 2.44	21.93 ± 1.21
F. deltoidea 1000 mg/kg/b.w.	23.56 ± 2.18	19.86 ± 1.53 (15.70)**	19.62 ± 1.00 (16.72)**	20.10 ± 1.58 (14.69)**
Metformin 500 mg/kg/b.w.	27.18 ± 3.78	19.67 ± 3.95 (27.63)*	14.57 ± 4.96 (46.39)***	13.18 ± 3.72 (51.57)***

Note: Values in bracket indicate percentage of blood glucose reduction relative to 0-hour of the respective treatment group. *p < 0.05, **p < 0.01 and ***p < 0.001 compared to 0 hour of the respective group

glucose after 4 and 6 hours of administration whereas extract at dose of 1000 mg/kg significantly reduced postprandial blood glucose level after 2, 4 and 6 hours of administration compared to the 0 hour. In contrast, extract at dose of 500 mg/kg did not reduce postprandial blood glucose even though until 6 hours post administration. Metformin significantly reduced postprandial hyperglycemia after 2, 4 and 6 hours of administration.

ORAL GLUCOSE TOLERANCE TEST

The effects of various doses of ethanolic extract of *F. deltoidea* on glucose tolerance activity in streptozotocin-induced diabetic rats are shown in Table 3. All group of rats showed almost similar blood glucose level at 0 min. The highest increase in blood glucose level was observed 30 min after glucose administration in all groups with the changes of blood glucose level were 1.47-fold, 1.37-fold, 1.46-fold and 1.36-fold and 1.16-fold in control group, ethanolic extract 100 mg/kg, ethanolic extract 500 mg/kg, ethanolic extract 1000 mg/kg and metformin group, respectively compared to glucose administration time (0 min) of respective treatment group. There was no reduction in blood glucose level in groups treated with ethanolic extracts (all doses) compared to the respective time of control group. In contrast, metformin treated group showed a significant reduction of blood glucose concentration at 30, 60, 120 and 180 minutes after glucose loaded compared to respective time from control group (Table 3).

Areas under the glucose curve ($AUC_{Glucose}$) for each individual rat, calculated to determine the increment of blood glucose concentration from 0 to 180 minutes is shown in Table 4. The results showed that, extract at dose of 100 mg/kg significantly attenuated $AUC_{Glucose}$ value by 48.87% ($p<0.05$) compared with control group. However, the attenuation of $AUC_{Glucose}$ value by such extracts was less than metformin which attenuated $AUC_{Glucose}$ value by 94.78% ($p < 0.001$) relative to control group.

DISCUSSION

F. deltoidea has been used for long time as traditional medicine to counter high blood glucose. However, scientific studies to evaluate its efficacy and possible mode of action are still lacking. In the present study, the potential

TABLE 3. Effect of ethanol extract of *F. deltoidea* on blood glucose level during oral glucose tolerance test in streptozotocin-induced diabetic rats

Treatment group	Blood glucose level (mmol/L) (mean ± SD)					
	-30 min	0 min	30 min	60 min	120 min	180 min
Control	17.11 ± 1.95	18.53 ± 1.30	27.33 ± 2.95	24.76 ± 3.50	19.11 ± 3.70	16.93 ± 3.81
F. deltoidea 100 mg/kg/b.w.	18.79 ± 2.69	20.72 ± 2.53	28.38 ± 4.05	24.89 ± 2.76	20.13 ± 2.16	17.97 ± 1.82
F. deltoidea 500 mg/kg/b.w.	17.30 ± 2.69	18.95 ± 2.57	27.61 ± 2.77	26.61 ± 3.01	22.53 ± 1.33	17.90 ± 1.87
F. deltoidea 1000 mg/kg/b.w.	17.73 ± 1.94	19.63 ± 1.58	26.75 ± 1.92	25.35 ± 3.45	19.60 ± 1.53	15.74 ± 1.75
Metformin 500 mg/kg/b.w.	17.73 ± 1.72	18.86 ± 2.60	21.87 ± 3.54 (19.98%)**	19.56 ± 2.60 (21.00%)**	12.54 ± 3.59 (34.38%)**	8.92 ± 4.24 (47.31%)**

Note: Values in bracket indicate percentage of blood glucose reduction relative to respective time of control group. **p<0.01 compared with respective time of control group

TABLE 4. Value of area under glucose curve during oral glucose tolerance test in the presence of ethanol extract of *F. deltoidea*

Treatment group	$AUC_{Glucose}$ value (mmol/L) (mean ± SD)	95 % CI (mmol/L) (mean ± SD)
Control	802.50 ± 320.90	404.00 – 1201.00
F. deltoidea 100 mg/kg/b.w.	410.30 ± 119.00 (48.87)*	300.20 – 520.30
F. deltoidea 500 mg/kg/b.w.	635.50 ± 81.64	534.10 – 736.90
F. deltoidea 1000 mg/kg/b.w.	486.00 ± 166.60	346.80 – 625.30
Metformin 500 mg/kg/b.w.	41.88 ± 16.26 (94.78)***	21.69 – 62.07

Note: Values in bracket indicate percentage of $AUC_{Glucose}$ attenuation relative to control group. *p < 0.05 and ***p < 0.001 compared with control group

antihyperglycemic property of ethanolic extract of *F. deltoidea* was evaluated at different prandial state; fasting, postprandial and glucose loaded state. Antihyperglycemic test in fasting and postprandial state were performed to evaluate whether extract has the tendency to counter fasting and post prandial hyperglycemia respectively. Likewise, glucose tolerance test was done to evaluate whether the extract has the potential to improve glucose tolerance activity. A significant reduction of blood glucose level was found after supplementation by *F. deltoidea* ethanolic extract at the mentioned prandial states, suggesting that there is possibility of presence of antihyperglycemic compounds in the studied extract.

In order to challenge the potential of ethanolic extract of *F. deltoidea* in reducing blood glucose concentration, conventional antihyperglycemic agent, metformin was used as a positive control. Metformin which is belonging to biguanides group has been reported to be an effective antihyperglycemic agent with the main mechanism is through enhancement of glucose uptake into muscle cells and reduction of hepatic gluconeogenesis, thereby reducing glucose concentration in blood stream (Chehade & Mooradian 2000).

Although less potent than metformin, ethanolic extract of *F. deltoidea* shows the ability to reduce fasting blood glucose in streptozotocin-induced diabetic rats. However, this reduction did not reach normoglycemic level even after 6 hours of extract administration. Metformin reduced fasting blood glucose to less than normoglycemic level 4 hours after administration. The less potential of fasting antihyperglycemic activity of ethanolic extract of *F. deltoidea* compared to metformin could be due to the presence of a mixture of bioactive and non-bioactive compounds in the extracts. This would reduce the concentration of active compounds in the extract and decrease the ability of the extracts to reduce fasting blood glucose. In contrast, metformin consists of single constituent and its antihyperglycemic activity has been scientifically proven (Chehade & Mooradian 2000). Maximum fasting antihyperglycemic activity was shown by moderate dose of extract, 500 mg/kg after 4 hours of extract administration followed by the lowest dose, 100 mg/kg and the highest dose, 1000 mg/kg. The latter two doses, 100 mg/kg and 1000 mg/kg possess similar degree of post prandial blood glucose reduction after 4 and 6 hours of extract administration.

In postprandial antihyperglycemic evaluation, the lowest dose, 100 mg/kg significantly reduced post prandial hyperglycemia after 4 hours of administration whereas the highest dose, 1000 mg/kg starts to reduce hyperglycemia as early as 2 hours after administration (Table 2). This observation indicates that the onset of antihyperglycemic effect by extract at low dose is slower than high dose. This could be due to the less amount of bioactive constituent(s) presence in low dose of extract and hence it takes long time for bioactive constituent(s) in the extract to enter circulation and reach the target tissue. The highest postprandial antihyperglycemic activity was shown at dose of 100 mg/kg and followed by 1000 mg/kg. Unlike such doses, the moderate dose, 500 mg/kg did not show postprandial antihyperglycemic activity. In this evaluation, neither extracts nor did metformin reduced postprandial hyperglycemia to normoglycemic level even after 6 hours of administration. There is possibility that, it takes more than 6 hours for the extracts or metformin to enter circulation and reach the target tissue and brings the postprandial antihyperglycemic effect. Of three doses evaluated, the lowest dose, 100 mg/kg appeared to be the most effective dose as it caused maximum lowering effect of postprandial hyperglycemia in streptozotocin-induced diabetic rats.

In oral glucose tolerance study, extract at low dose, 100 mg/kg significantly attenuated $AUC_{Glucose}$ value compared to the control group. This suggests that such dose of extract has the ability to improve glucose tolerance activity in streptozotocin-induced diabetic rats. Nevertheless, this activity appeared to be less effective as compared with metformin. The efficiency of metformin in improving glucose tolerance activity was almost double from that seen in ethanolic extract 100 mg/kg (Table 4). This observation indicates that the glucose tolerance activity shown by such extract was not potent as shown by metformin. This may be due to the presence of compounds in *F. deltoidea* ethanolic extracts which do not possess glucose tolerance activity. Therefore, to enhance the effectiveness of such extract in improving glucose tolerance, further works are needed to be carried out to isolate the bioactive constituent(s) with glucose tolerance activity from the extract. Of three doses evaluated, the lowest dose, 100 mg/kg seem to be most potent in improving glucose tolerance activity in streptozotocin-induced diabetic rats. The remaining doses, 500 mg/kg and 1000 mg/kg did not produced expected higher glucose tolerance activity than 100 mg/kg. This could be due to the presence of other compounds in higher doses which may antagonist or interfering the glucose tolerance activity.

Antihyperglycemic plants mediate fasting and postprandial antihyperglycemic activity through various mechanisms such as stimulating insulin secretion from pancreatic beta cells (Gireesh et al. 2009), augmentation of glucose transport into peripheral cells (Jung et al. 2009; Anandharajan et al. 2005) and inhibition of α-glucosidase activity in small intestine (Nickavar et al. 2008). In the present study, the mechanism by which ethanolic extract of *F. deltoidea* mediates antihyperglycemic activity is not elucidated. There is possibility that ethanolic extract of *F. delttoidea* mediates antihyperglycemic activity through the mentioned mechanisms. However, further evaluations are needed to be carried out to confirm this suggestion. The control of postprandial hyperglycemia is one of the beneficial therapies for management of diabetes mellitus (Kim et al. 2005) along with medical nutrition therapy, oral hypoglycaemic agents and insulin therapy (David 2005). Therefore, the uses of plants with postprandial antihyperglycemic property such as *Mucuna pruriens* (Anusha et al. 2008) and *Cynara cardunculus* (Nomikos et al. 2007) as well as plants with glucose tolerance property such as *Helicteres ixora* (Venkatesh et al. 2004) and *Tournefortia hartwegiana* (Ortiz-andrade et al. 2007) may benefits the diabetes patients in controlling postprandial hyperglycemia. Based on the results of the present study, it is suggested that *Ficus deltoidea* may advantageous the diabetes patients in the management of postprandial hyperglycemia as well as diabetes mellitus.

This study had shown that ethanolic extract of *Ficus deltoidea* possess fasting and postprandial antihyperglycemic activity as well as glucose tolerance activity in streptozotocin-induced diabetic rats. Therefore, it is suggested that *Ficus deltoidea* could be used as dietary adjunct to counter hyperglycemia in diabetes patients and has the potential to be developed as new oral antihyperglycemic agent for the treatment of diabetes mellitus.

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