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Antihyperglycemic Activity of *F. deltoidea* Ethanolic Extract in Normal Rats

(Aktiviti Antihiperglisemik Ekstrak Ethanol *Ficus deltoidea* di dalam Tikus Normal)

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ABSTRACT

Ficus deltoidea *is one of the common medicinal plants used in Malaysia. This epiphytic plant, from the Moraceae family has been claimed to have antidiabetic property. However, scientific evidence to confirm its efficacy is still lacking. The present study was undertaken to evaluate the effect of ethanolic extract of* F. deltoidea *on glucose level in normal rats at different prandial state. The results showed that, all doses of ethanolic extract of* F. deltoidea *reduced fasting blood glucose particularly after 6 h of administration. Interestingly, the extract did not produce severe hypoglycemia as shown by its comparable effect with metformin. Likewise, postprandial hyperglycemia was also significantly reduced particularly after 4 and 6 h of administration. Furthermore, extract was used at a dose of 1000 mg/kg b.w., reduced postprandial hyperglycemia similar to metformin. This suggests that postprandial antihyperglycemic mechanism of this extract is mediated through enhancement of glucose uptake into muscle cells and reduction of hepatic gluconeogenesis. Glucose tolerance activity was also significantly improved in the presence of ethanolic extract of* F. deltoidea. *From this study, it is suggested that ethanolic extract of* F. deltoidea *reduced postprandial hyperglycemia and improves glucose tolerance activity in normal rats.*

Keywords: F. deltoidea*; glucose tolerance activity; postprandial antihyperglycemia*

ABSTRAK

Ficus deltoidea *merupakan salah satu tumbuhan ubatan yang lazim di Malaysia. Pokok epifit ini, daripada keluarga Moraceae dipercayai mempunyai sifat antidiabetik. Walau bagaimanapun, bukti saintifik untuk mengesahkan keberkesanannya masih kurang. Kajian ini dijalankan untuk menilai kesan ekstrak ethanol* F. deltoidea *terhadap aras glukosa di dalam tikus normal pada keadaan prandial yang berbeza. Keputusan menunjukkan bahawa, kesemua dos ekstrak menurunkan flukosa darah puasa terutamanya selepas 6 jam pengambilan. Yang menariknya, ekstrak ini tidak menyebabkan hipoglisemia terus sebagaimana yang ditunjukkan oleh kesannya yang sebanding dengan metformin. Begitu juga, hiperglisemia posprandial turut diturunkan secara signifikan terutamanya 4 dan 6 jam selepas pengambilan. Tambahan lagi, ekstrak digunakan pada dos 1000 mg/kg b.w. telah menunjukkan penuruan hiperglisemia posprandial sama seperti metformin. Ini mencadangkan bahawa mekanisme antihiperglisemia posprandial ekstrak ini diperantarakan melalui peningkatan pengambilan glukosa ke dalam sel otot dan penurunan glukoneogenesis hati. Aktviti toleransi glukosa juga diperbaiki secara signifikan dengan kehadiran ekstrak ethanol* F. deltoidea. *Daripada kajian ini, dicadangkan bahawa ekstrak ethanol* F. deltoidea *menurunkan hipeerglisemia posprandial dan memperbaiki aktiviti toleransi flukosa di dalam tikus normal.*

Kata kunci: Aktiviti toleransi glukosa; antihiperglisemia posprandial; F. deltoidea

INTRODUCTION

Diabetes mellitus is a metabolic disease characterized by persistent hyperglycemia in fasting and/or postprandial state with disturbances in carbohydrate, fat and protein metabolism resulting from defects of insulin secretion or insulin action or combination of these two factors (WHO 1999; Zanatta et al. 2007). It remains a major global health problem in most countries even though there are plenty of antidiabetic agents available in the market. In addition, it is the first leading causes of death in developed country and has been an epidemic in many developing countries including Malaysia (Ooyub et al. 2004). Globally, the prevalence of diabetes for all groups of age was estimated to be 2.8% in 2000 and this number is estimated to rise by 4.4% in 2030. Recent estimation indicates that there were 171 diabetes sufferers in the world in 2000 and this is projected to increase to 366 million by 2030 (Wild et al. 2004). In Malaysia, prevalence of diabetes mellitus has steadily increased with an estimated number of people with diabetes was 0.65% in 1960 and 2% in 1982 (Ooyub et al. 2004). The National Health and Morbidity Survey (NHMS) I, II and III which was conducted in 1986, 1996 and 2006 reported the prevalence of diabetes were 6.3%, 8.3% and 14.9%, respectively in subjects above 30 years (Zanariah et al. 2006).

Currently, treatment of diabetes mellitus involves exercise, diet therapy, insulin therapy and oral antidiabetic agents such as sulphonylureas, biguanides, thiazolidinediones and α-glucosidase inhibitor (Kimmel & Inzucchi 2005; Li et al. 2005). Despite of their effectiveness in reducing hyperglycemia, the use of these drugs are associated with non-desirable side effects. For instant, sulphonylureas treatment is associated with hypoglycemia and weight gain (Kimmel & Inzucchi 2005); α-glucosidase inhibitor causes hepatotoxicity and gastrointestinal adverse reaction (Andrade et al. 1998; Coniff & Krol 1997). Therefore, searching for new effective antihyperglycemic agents with minimal side effects should be continued. Plants have been widely used for searching of new antidiabetic agents as it is proposed to be safe and have minimal side effects (Li et al. 2005).

F. deltoidea, from the Moraceae family is commonly used as a medicinal plant in Malaysia (Mat-Salleh & Latif 2002). This plant which is a native to Southeast Asia and Philiphines (Forest et al. 2003) are also used to treat other kind of ailments. For example, the roots and leaves have been used to relieve headache and fever (Mat-Salleh & Latif 2002). The fruits are chewed to relieve toothache and decoction of the whole plants was used as herbal drink by women after birth to strengthen the uterus (Sulaiman et al. 2008). Recent study on aqueous extract of *F. deltoidea* indicated the antinociceptive activity (Sulaiman et al. 2008) and antiulcerogenic activity against ethanol-induced gastric mucosal injury in rats (Siti Fatimah Zahra et al. 2009). In addition, Hakiman and Maziah (2009) have found that aqueous extract of different *F. deltoidea* accessions possess non enzymatic and enzymatic antioxidant activities. Study on chemical constituents of *F. deltoidea* by Din et al. (2002) reported the absence of alkaloid, triterpine and saponin in *F. deltoidea* leaves. However, Zunoliza et al. (2009) has reported that *F. deltoidea* var. *angustifolia* contains polyphenols, flavonoids and tannins. They also found that methanolic extract of *F. deltoidea* var. *angustifolia* has higher metabolites content than aqueous extract.

Based on ethnobotanical approaches, *F. deltoidea* has been claimed to possess antidiabetic properties, and it has been used traditionally as a treatment for diabetes. Nevertheless, scientific evidence to confirm its efficacy and its possible mode of action is still lacking. Therefore, the present study was undertaken to evaluate the potential of ethanolic extract of *F. deltoidea* to reduce blood glucose level in normal rats at different prandial states.

Materials and Methods

Chemicals

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

Plant Materials and Extraction

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

Animals

Adult Sprague Dawley rats (200-250 gram) which were used in the study were breed in house at Animal House of Malaysian Nuclear Agency. 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). Experimental animals 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 *F. deltoidea* suspended in 1% CMC at doses of 100, 500 and 1000 mg/kg b.w., respectively. Group V was treated with metformin suspended in 1% CMC at the dose of 500 mg/kg b.w.

Hypoglycemic and Postprandial Antihyperglycemic Test

In hypoglycemic test, rats were fasted 12 h prior to test whereas in postprandial antihyperglycemic test, rats were fasted 1 h prior to test. After fasting period, the rats were given orally with either *F. deltoidea* ethanolic extract or metformin using intragastric gavage. Blood were collected from the tail vein just before (0 h) and after 2, 4 and 6 h administration of extract or metformin for the measurement of blood glucose concentration.

Oral Glucose Tolerance Test (OGTT)

For OGTT evaluation, the rats were fasted for 12 h and blood was taken 30 min before administration of *F. deltoidea* or metformin. Thirty minutes later, the rats from all groups were given glucose (1.5 g/kg) orally. Blood were collected from the tail vein just prior to glucose administration (0 min), 30, 60, 120 and 180 min after glucose loading. Total glyceamic responses to OGTT were calculated from respective areas under the glucose curve ($AUC_{Glucose}$) during the 180 min 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).

BIOCHEMICAL ANALYSIS

The glucose level was determined by using electronic glucometer, Accu Check Advantage from Roche Diagnostic (Indianapolis, USA).

STATISTICAL ANALYSIS

The results were expressed as mean ± standard deviation of seven rats. All data were analysed using one way ANOVA and followed by Tukey multiple comparison test. Groups mean were considered significantly different at the level of $p<0.05$.

RESULTS

HYPOGLYCEMIC TEST

Table 1 shows the effect of ethanolic extract of *F. deltoidea* on fasting blood glucose in normal rats. The extract at doses of 500 and 1000 mg/kg b.w., significantly reduced blood glucose level after 2, 4 and 6 h of administration whereas extract at a dose of 100 mg/kg b.w., significantly reduced blood glucose level after 6 h of administration only. The hypoglycemic effect of the extracts at doses of 500 and 1000 mg/kg b.w. after 6 h of administration was comparable to the metformin group. Among three doses, the highest dose which is 1000 mg/kg b.w. seem to be the most potent in reducing fasting blood glucose level in normal rats.

POSTPRANDIAL ANTIHYPERGLYCEMIC TEST

The postprandial antihyperglycemic effects of ethanolic extract of *F. deltoidea* in normal rats are shown in Table 2. The results showed that extract at 100 and 500 mg/kg b.w., significantly reduced blood glucose level after 4 and 6 h of administration whereas at 1000 mg/kg b.w. significantly reduced blood glucose level after 2, 4 and 6 h of administration. The postprandial antihyperglycemic effect possess by dose of 1000 mg/kg b.w. was comparable to metformin group which significantly reduced postprandial hyperglycemia after 2, 4 and 6 h of administration. Among the three doses evaluated, the highest dose which is 1000 mg/kg b.w. appeared to be the most effective dose in reducing postprandial hyperglycemia in normal rats.

TABLE 1. Effect of ethanolic extract of *F. deltoidea* on fasting blood glucose concentration in normal rats

Treatment group	Blood glucose level (mmol/L)			
	0 hr	2 hr	4 hr	6 hr
Control	4.93 ± 0.26	4.83 ± 0.48	4.78 ± 0.31	4.83 ± 0.50
F. deltoidea (100 mg/kg)	5.02 ± 0.62	4.65 ± 0.70	4.51 ± 0.67	4.14 ± 0.67 (17.6%) **
F. deltoidea (500 mg/kg)	5.18 ± 0.36	4.43 ± 0.91 (14.5%) *	4.17 ± 0.89 (19.6%) **	3.93 ± 0.68 (24.3%) **
F. deltoidea (1000 mg/kg)	5.18 ± 0.38	3.99 ± 0.64 (22.9%) **	4.29 ± 0.64 (17.3%) **	3.81 ± 0.43 (26.5%) **
Metformin (500mg/kg)	4.43 ± 0.41	4.083 ± 0.61	3.96 ± 0.62	3.28 ± 0.38 (26.1%) **

Results were expressed as mean ± standard deviation of seven rats. Values in bracket indicate percentage of blood glucose reduction relative to 0-hour of the respective treatment group. *p<0.05 and **p<0.01 compared to 0 hour of the respective group

TABLE 2. Effect of ethanolic extract of *F. deltoidea* on postprandial glucose concentration in normal rats

Treatment group	Blood glucose level (mmol/L)			
	0 hr	2 hr	4 hr	6 hr
Control	8.98 ± 0.46	8.37 ± 1.02	8.35 ± 0.99	8.08 ± 1.30
F. deltoidea (100 mg/kg)	8.19 ± 0.38	7.771 ± 0.42	6.81 ± 0.70 (16.8%) **	6.63 ± 0.25 (19.1%) **
F. deltoidea (500 mg/kg)	7.83 ± 0.31	7.53 ± 0.47	6.70 ± 0.26 (14.4%) **	6.78 ± 0.59 (13.4%) **
F. deltoidea (1000 mg/kg)	8.19± 0.66	7.40 ± 0.56 (10.0%) *	6.70 ± 0.65 (18.2%) **	6.92 ± 0.38 (15.5%) **
Metformin (500 mg/kg)	8.20 ± 0.43	7.11 ± 0.63 (13.3%) **	6.93 ± 0.68 (15.5%) **	6.52 ± 0.90 (20.5%) **

Results were expressed as mean ± standard deviation of seven rats. Values in bracket indicate percentage of blood glucose reduction relative to 0-hour of the respective treatment group. *p<0.05 and **p<0.01 compared to 0 hour of the respective group

ORAL GLUCOSE TOLERANCE TEST

All group of rats showed similar baseline (0 min) of blood glucose levels (Table 3). The highest increase in blood glucose level in all groups was observed 30 min after glucose administration. The changes of blood glucose level were 1.75-fold, 1.68-fold, 1.77-fold, 1.76-fold and 1.17-fold in control group, extract 100 mg/kg b.w., extract 500 mg/kg b.w., extract 1000 mg/kg b.w. and metformin group, respectively as compared to glucose administration time (0 minutes) of the respective treatment group.

Blood glucose level of groups treated with all doses of ethanolic extract was significantly reduced after 120 and 180 min of glucose administration compared to respective time from the control group. Meanwhile, metformin treated group showed a significant reduction of blood glucose level after 60, 120 and 180 min of glucose administration as compared to respective time from the control group (Table 3).

Areas under the glucose curve ($AUC_{Glucose}$) for each individual rat was calculated to determine the increment of blood glucose concentration from 0 to 180 min (Table 4). Extract at doses of 100, 500 and 1000 mg/kg b.w. significantly attenuated $AUC_{Glucose}$ value by 37.39% ($p<0.01$), 32.46% ($p<0.05$), and 32.45% ($p<0.05$) as compared with control group. However, the attenuation of $AUC_{Glucose}$ value by such extracts was less than metformin which attenuated $AUC_{Glucose}$ value by 89.11% ($p<0.001$) relative to the control group. Of the three doses evaluated, the lowest dose which is 100 mg/kg b.w. was found to be most potent in improving glucose tolerance activity in normal rats.

DISCUSSION

F. deltoidea has been used for long time as a traditional medicine to counter high blood glucose. However, scientific studies to evaluate its efficacy and possible mode of action are still lacking. Only two studies on *F. deltoidea* has been done which reports glucose lowering effect of aqueous extract of this plant in normal rats (Aminudin et al. 2007) and mild diabetic rats (Adam et al. 2007).

In order to challenge the potential of ethanolic extract of *F. deltoidea* in reducing blood glucose concentration, conventional antidiabetic drug, metformin was used as positive control. Metformin which belongs to biguanides group has been reported to be an effective antihyperglycemic agent and the main mechanism is through enhancement of glucose uptake into muscle cells and reduction of hepatic glucose production, thereby reducing circulation glucose concentration (Hawley et al. 2002).

TABLE 3. Effect of ethanolic extract of *F. deltoidea* on glucose tolerance activity in normal rats

Treatment group	Time (min)					
	-30	0	30	60	120	180
Control	4.82 ± 0.56	5.08 ± 0.31	8.91 ± 0.76	7.92 ± 1.08	6.01 ± 0.68	5.32 ± 0.68
F. deltoidea 100 mg/kg	4.78 ± 0.50	4.98 ± 0.74	8.35 ± 1.12	7.53 ± 0.73	3.95 ± 0.68 (34.28%) **	3.68 ± 0.36 (30.83%) **
F. deltoidea 500 mg/kg	4.37 ± 0.57	5.08 ± 0.82	9.00 ± 0.77	7.70 ± 1.33	4.57 ± 0.66 (23.96%) **	4.30 ± 0.54 (24.81%)*
F. deltoidea 1000 mg/kg	4.33 ± 0.41	4.58 ± 0.39	8.05 ± 0.73	7.47 ± 1.46	4.03 ± 0.53 (32.95%) **	4.17 ± 0.45 (21.62%)*
Metformin 500 mg/kg	4.56 ± 0.48	4.88 ± 0.44	5.74 ± 0.55 (35.58%)**	5.09 ± 0.55 (35.73%)**	4.23 ± 0.50 (29.62%)**	4.04 ± 0.29 (24.06%)*

Results were expressed as mean ± standard deviation of seven rats. Values in bracket indicate percentage of blood glucose reduction relative to respective time of control group. *p<0.05 and **p<0.01 compared with respective time of control group.

TABLE 4. Value of area under glucose curve during the oral glucose tolerance test

Treatment group	$AUC_{Glucose}$ value (mmol/L)	95% CI (mmol/L)
Control	328.70 ± 115.70	246.0 – 411.4
F. deltoidea (100 mg/kg)	205.8 ± 38.5 (37.39%) **	17.2 – 241.4
F. deltoidea (500 mg/kg)	222.0 ± 58.5 (32.46%) *	167.9 – 276.1
F deltoidea (1000 mg/kg)	222.1 ± 70.7 (32.435) *	156.7 – 287.6
Metformin (500 mg/kg)	35.8 ± 17.9 (89.11%) ***	20.9 – 50.8

Data were expressed as mean ± standard deviation of seven rats. Values in bracket indicate percentage of $AUC_{Glucose}$ reduction relative to control group. *p<0.05, **p<0.01 and ***p<0.001 compared with control group

In this study, the evaluation of antihyperglycemia of ethanolic extract of *F. deltoidea* was evaluated in different prandial state; fasting, postprandial and post glucose loaded state. Hypoglycemic test in fasting state was done to evaluate whether the extract has a tendency to produce severe hypoglycemia. The test on postprandial antihyperglycemia was done to evaluate the potential of the extract to challenge postprandial hyperglycemia whereas post glucose loaded antihyperglycemia test was done to evaluate the potential of extract to improve glucose tolerance activity. In the present study, significant reduction of blood glucose level by *F. deltoidea* ethanolic extract at different prandial state suggests the presence of antihyperglycemic compounds in ethanolic extract of this plant.

The results from this study showed that, ethanolic extract of *F. deltoidea* at all doses has the ability to produce hypoglycemic effect in rats with fasting condition particularly after 6 h of administration. The degree of blood glucose reduction produced by extract at doses of 500 and 1000 mg/kg b.w. was comparable to the metformin treated group. This result indicates that the extract did not produce severe hypoglycemia while reducing fasting blood glucose. This is a desirable feature as it has been noted that hypoglycemia or low blood sugar level can causes seizures, coma, accidents, or death and may even induce permanent brain damage (Ryan & Becker 1999).

In the evaluation of postprandial antihyperglycemia, extract at low and moderate dose, 100 mg/kg b.w. and 500 mg/kg b.w. significantly reduced blood glucose after 4 and 6 h of administration whereas the highest dose, 1000 mg/kg b.w. reduced blood glucose as early as 2 hours after administration (Table 2). This observation indicates that the extract at low dose takes longer time to reduce postprandial blood glucose. This is probably due to less amount of bioactive constituent(s) present in the low dose of extract. Extract at the dose of 1000 mg/kg b.w. showed similar potential and trend of postprandial antihyperglycemic activity with metformin 500 mg/kg b.w. This result suggests that, there is a possibility that ethanolic extract mediates postprandial antihyperglycemic activity through the similar mechanism as metformin, which enhances glucose uptake into muscle cells and reduced hepatic gluconeogenesis.

In oral glucose tolerance study, all doses of the extract significantly attenuated $AUC_{Glucose}$ value compared to the control group. This suggests that ethanolic extract of *F. deltoidea* has the ability to improve glucose tolerance activity in normal rats. Nevertheless, this activity was less effective than metformin as it was shown that, the efficiency of metformin in improving glucose tolerance activity was greater than ethanolic extract. This observation indicates that the glucose tolerance activity produced by the extract was not as potent as metformin. This could be due to *F. deltoidea* extracts contain a mixture of active and non-active compounds which reduce the concentration of active compounds and decrease the ability to improve glucose tolerance activity. Therefore, to enhance the effectiveness of such extract in improving glucose tolerance, further works to be carried out to isolate the bioactive compounds from the extract. Among three doses that have been evaluated, the lowest dose, 100 mg/kg b.w. possesses the highest glucose tolerance activity. The remaining doses, 500 and 1000 mg/kg b.w. did not produced expected higher glucose tolerance activity than 100 mg/kg. At the higher dose of ethanolic extract, the presence of non-bioactive compounds may antagonist or interfere the glucose tolerance activity.

Numerous plants have been reported to possess antihyperglycemic activity such as *Aegle marmelos* (Kesari et al. 2006) and *Leandra lacunosa* (Cunha et al. 2008). These plants mediate such activity through various mechanisms such as by stimulating insulin release from pancreatic beta cells (Gireesh et al. 2009), augmentation of glucose transport into adipocytes and muscle (Anandharajan et al. 2005; Jung et al. 2009) or combination of both mechanisms (Gray & Flatt 1998), reducing glucose production from liver (Hundal et al. 2000) and delaying glucose absorption from small intestine through the inhibition of α-glucosidase enzymes (Coniff & Krol 1997; Uebanso et al. 2007). The mechanisms by which ethanolic extract mediates the antihyperglycemic activity were studied and it was found that *F. deltoidea* ethanolic extract significantly stimulated insulin secretion from pancreatic cell line (unpublished data), enhanced glucose uptake by liver (Adam et al. 2009) and peripheral cells (unpublished data), and inhibited α-glucosidase enzymes in small intestine (Adam et al. 2010). Combinations of these mechanisms have partly evidenced the antihyperglycemic activity of *F. deltoidea* ethanolic.

The control of postprandial hyperglycemia is one of the beneficial therapy for management of type II diabetes mellitus (Kim et al. 2005) along with nutrition, oral hypoglycaemic and insulin therapies (David 2005). In addition, controlling postprandial hyperglycemia could also prevent the development of macro-and microvascular complications associated with diabetes (Baron 1998). The use of plants with postprandial antihyperglycemic property such as *Mucuna pruriens* (Bhaskar 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 diabetic patients in controlling postprandial hyperglycemia. Based on the results of the present study, it is suggested that *F. deltoidea* could be included as an antihyperglycemic plant and may be advantageous to the diabetic patients in the controlling of postprandial hyperglycemia.

Conclusions

From this study, it has been shown that ethanolic extract of *F. deltoidea* possess postprandial antihyperglycemic and glucose tolerance activity in normal rats. In addition, *F. deltoidea* does not cause severe hypoglycemia. Therefore,

it is suggested that *F. deltoidea* can be used as a dietary adjunct to counter hyperglycemia and has the potential to be developed as new oral antidiabetic agent for the treatment of diabetes mellitus.

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