Effects of Flower Extract from Lotus (*Nelumbo nucifera*) on Hypoglycemic and Hypolipidemic in Streptozotocin-induced Diabetic Rats

Supasorn Sakuljaitrong, Nopparat Buddhakala, Sanong Chomko and Chusri Talubmook

Abstract— This study was aimed to investigate an acute toxicity and effects of *Nelumbo nucifera* flower extract (NNFE) on hyperglycemic and hypolipidemic effects in streptozytocin-induced diabetic rats. *In vivo* acute toxicity study of NNFE was carried out by once oral administration various doses (0, 500, 1000, 1500 and 2000 mg/kg) of the extract to healthy male adult Wistar rats. Sign or symptom of toxicity and mortality were examined within 24 h and further period of 14 days. The studies of effects of the extract on hypoglycemic and hypolipidemic activities were performed by given the extract at a dose of 250 mg/g b.w. to STZ-induced diabetic rats orally and daily for 8 weeks. The results revealed that the extract did not produce any signs or symptoms of toxicity and the mortal rats were not found during the period of observation. Furthermore, the extract at a dose of 250 mg/kg significantly ($p<0.05$) decreased the levels of fasting blood glucose (FBG), total cholesterol (TC), triglycerides (TG), low density lipoprotein (LDL), and blood urea nitrogen (BUN) but increased high density lipoprotein (HDL) in the NNFE- treated diabetic rats compared to diabetic controls. However, the extract did not alter creatinine in diabetic treated rats compared to diabetic controls. These findings indicate that NNFE had non acute toxicity but possesses hypoglycemic and hypolipidemic activities. NNFE is one of alternative beneficial products in a treatment of diabetes.

Index Terms— *Nelumbo nucifera*, *Acute toxicity*, *Diabetic rats*, *Hypoglycemic*, *Hypolipidemic*

1 INTRODUCTION

Diabetes mellitus (DM) is a metabolic disorder disease in which the carbohydrate and lipid metabolism is improperly regulated by insulin [1]. Diabetes mellitus is characterized by constant high levels of blood glucose. Diabetes mellitus is known to cause hyper-lipidemia through various metabolic derangements. Among several metabolic derangements, insulin deficiency has been known to stimulate lipolysis in the adipose tissue and gives rise to hyperlipidemia and fatty liver. Thus, in diabetes hypercholesterolemia and hypertriglyceridemia often occurs [2].

Management of diabetes without any side effect is still a challenge to the medical system. This leads to increase the demand for complementary and alternative medicine with antidiabetic activity and without side effects [3].

The potential role of medicinal plants as hypoglycemic agents has been reported in many studies which supported to ethnobotanical surveys and use of traditional medicines in numerous cultures [4].

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Many indigenous Thai medicinal plants have been found and recommended for the treatment of diabetes such as *Piper sarmentosum* Roxb, *Tinospora crispa* Miers ex Hook.F &Thoms. [5], *Momordica charantin* Linn. [6], *Morus alba* Linn., *Annona squamosa* Linn. [7], *Coscinium fenestratum* (Gaertn.) Colebr. [8], [9], *Butea monosperma* [10] and *Nelumbo nucifera* Gaertn. [11], [12], [13], [14].

Lotus (*Nelumbo nucifera* Gaertn.) is a perennial water plant grown as an ornamental plant and is one of the popular traditional folk herbs used in Thailand. Its roots are used as a vegetable. In addition, leaves, stems, seeds and other parts of the plant are edible and are thought to have multiple medicinal properties [15]. The traditional medicine systems advocate different therapeutic effects of this plant. Rhizome is considered to be nutritive, demulcent, diuretic and cholagogue and is used to treat piles, dyspepsia and dirrhorea [16]. The rhizome extract showed anti-diabetic [17], [18], anti-inflammatory properties due to presence of asteroidal triterpenoid [19], and anti-obesity attributes [15]. The leaves are known for their refrigerant, astringent and diuretic actions. This led to diverse applications such as using the leaves for diarrhea, high fever, hemorrhoids and leprosy [20], [21]. The leaves and flowers are useful to treat many bleeding disorders. Leaves and flowers are useful to treat for bleeding disorders and the consumption of flowers is recommended to promote the conception. In folk medicines, seeds are used in the treatment inflammation, cancer, skin diseases, leprosy, poison antidote and generally prescribed to children as diuretic and refrigerant [22]. In addition, flowers are useful to treat diarrehoea, cholera, fever, hepatopathy and hyperdipsia. Hyper-

lipidemia in rodents can be treated with lotus leaves [23], [24]. The stamens assist consolidation of kidney function and are particularly useful in the treatment of male sexual disorders and female leucorrhea [21]. Several pharmacologically activities, the isolated from various parts of *N. nucifera*., were found the main compounds; alkaloids, steroids, triterpenoids, flavonoids, glycosides and polyphenols [25], [26] , [19], [27], [28], [29], [30].

However the study on acute toxicity, the effects on lipid profile and kidney function of *N. nucifera* flowers extract (NNFE) in diabetic rats has been poorly studied. The purposes of this study were therefore designed to investigate acute toxicity and effects of *N. nucifera* flower extract (NNFE) on fasting blood glucose (FBG), lipid profile (total cholesterol, triglycerides, low-density lipoprotein, and high-density lipoprotein), and renal function (blood urea nitrogen and creatinine) in STZ-induced diabetic rats. The results from this study can be used for utilization in the traditional medicine for the diabetic patients.

2 Material and Methods

2.1 Plant Materials

Lotus flowers were collected from natural resource in Khonkaen Province, Northeastern, Thailand. The specimens were identified by The Plant Varieties Protection Division, Department of Agriculture, Ministry of Agriculture and Cooperatives, Thailand. They were deposited in the Department of Biology, Faculty of Science, Mahasarakham University, Thailand (Code: MSU.Sc-BI001).

2.2 Preparation of NNFE

The fresh lotus flowers were cut into pieces and dried in hot air oven at a temperature of 50°C for 72 hours. The dried flowers were subjected to sized reduction a coarse powder by using grinder. The dried flowers were macerated with 95% ethanol (Merck, Germany) for 7 days (1:10 w/v). The extract was evaporated by using a rotary evaporator (Heidolph Laborota 4000, Germany) followed by a freeze dryer (Christ Alpha 1-4, Germany) to get powder (15.26 w/w of dry flowers). The obtained 95% ethanolic extract of NNFE was stored at -20°C until being used.

2.3 Animals

Male *albino* Wistar rats weighing 200-250 g. purchasing from the National Laboratory Animal Centre, Mahidol University, Thailand were the animals used in the present study. They were kept in clean cages in an air conditioned room at 25±2°C with 12-h light/12-h dark cycle. The rats were maintained on standard pellet diet and tap water *ad libitum* and acclimatized for 7 days prior to the commencing experiments.

This study was conducted according to the guidelines of the Committee Care and Use of Laboratory Animal Resource, National Research Council Thailand, and preformed in accordance with the advice of the Institutional Animal Care and Use Committee, Maha sarakham University (MSU), Thailand (License No. 0005/2011).

2.4 Acute Toxicity Study

Healthy rats were randomly assigned to five groups with 8 rats in each; Group I: normal control rats administered with distilled water, Group II, III, IV, and V: rats administered with NNFE 500, 1000, 1500 and 2000 mg/kg respectively. NNFE or distilled water was once administered to the rats orally. Signs or symptoms of acute toxicity and the mortality rats were observed within 24 h and a further period for 14 days after the administration.

2.5 Induction of Diabetes

The rats were induced to be diabetes by a single intraperitoneal injection with 65 mg/kg of streptozotocin (Sigma Chemicals, St. Louis, MO) dissolved in fresh and cold 20 mM citrate buffer pH 4.5. [31]. After injection, they were provided with 2% sucrose solution as their drinking water for 48 hours to alleviate the severity after initial hypoglycemic phase. [32]]. Diabetes was confirmed three days after injection. The rats with fasting blood glucose (FBG) > 126 mg/dl were selected for the study.

2.6 Experimental Design

The rats were randomly assigned into four groups with eight rats in each; Group I: normal controls, Group II: diabetic controls, Group III: diabetic rats treated with 0.25 mg/kg b.w. glibenclamide (GB), and Group IV: diabetic rats treated with 250 mg/kg b.w. NNFE. The normal controls and diabetic controls were administered with 0.05% ethanol orally and daily. NNFE and GB were suspended in 0.05% ethanol prior to the oral administration using an orogastric tube.

2.7 Fasting Blood Glucose Study

The rats were randomly assigned into four groups with eight rats in each; Group I: normal controls, Group II: diabetic controls, Group III: diabetic rats treated with 0.25 mg/kg b.w. glibenclamide (GB), and Group IV: diabetic rats treated with 250 mg/kg b.w. NNFE. The normal controls and diabetic controls were administered with 0.05% ethanol orally and daily. NNFE and GB were suspended in 0.05% ethanol prior to the oral administration using an orogastric tube.

2.8 Lipid Profile and Renal Function Studies

Eight weeks after the administration, the rats were fasted over night and sacrificed under cervical dislocation technique. The blood sample was drawn from the rat hearts and then centrifuged with 3000 rpm for 10 min twice to separate blood serum. Lipid profile including total cholesterol (TC), triglycerides (TG), low-density lipoprotein (LDL), and high-density lipoprotein (HDL) and remal function including blood urea nitrogen (BUN) and creatinine were determined by using au-

tomatic analyzer with Asus model BT 2000 plus.

2.9 Statistical Analysis

Statistical analysis was carried out using One-way ANOVA followed by Scheffe's test. The criterion for statistical significance was *p*-values less than 0.05. All data were expressed as mean ± standard error of mean (SEM).

3 Results

3.1 Effect of NNFE on Acute Toxicity

Once oral administration of NNFE to male adult Wistar rats revealed that various doses (0, 500, 1,000, 1,500 and 2,000 mg/kg b.w.) of NNFE could not produced any signs or symptoms of toxicity and mortal rat was not found during the period of observation (24 h and 14 days).

3.2 Effect of NNFE on Fasting Blood Glucose

As shown in Fig. 1, repeated oral administration of NNFE at a dose of 250 mg/kg to the diabetic rats for 8 weeks showed that NNFE has no effect on FBG of normal controls and diabetic control rats. However, it significantly ($p<0.05$) reduced FBG in NNFE treated diabetic rats with a percentage reduction of 51.41±1.44% which was close to that in GB treated diabetic rats (54.22±1.89%).

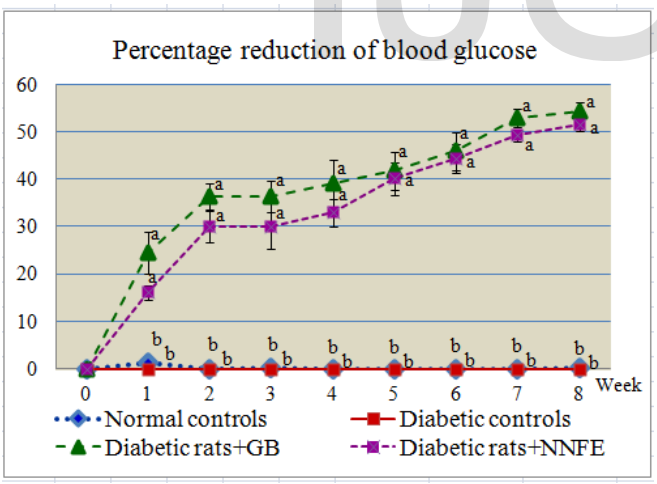

Fig. 1. The effect of NNFE on percentage reduction of FBG in normal controls, diabetic controls, diabetic rats treated with GB, and diabetic rats treated with NNFE.

3.3 Effect of NNFE on Lipid Profile

The Lipid profile affected by NNFE was depicted in Table 1 and Table 2.

Table 1, TC and TG increased in the diabetic controls were significantly ($p<0.05$) reduced in NNFE treated diabetic rats compared to that in diabetic controls and. NNFE also recovered TC and TG in the diabetic rats closely to normal controls. Moreover, NNFE exhibited the potential reduction of TC and TG significantly ($p<0.05$) greater than GB.

Table 2, HDL was significantly ($p<0.05$) decreased while LDL was significantly ($p<0.05$) increased in the diabetic controls compared to normal controls. However, the treatment of diabetes rats with NNFE that has potentially improves similar to treatment with the GB.

TABLE I
EFFECT OF NNFE ON LIPID PROFILE (TOTAL CHOLESTEROL (TC) AND TRIGLYCERIDE (TG)

Groups	Lipid profile (mg/dl)	
	TC	TG
I. Normal controls	86.17±2.64^{a}	97.67±3.59^{a}
II. Diabetic controls	135.67±2.51^{c}	190.67±2.14^{c}
III. Diabetic rats+GB	114.17±1.64^{b}	145.00±4.08^{b}
IV. Diabetic rats+NNFE	97.33±1.86^{a}	108.50±3.99^{a}

Data were expressed as mean ± S.E.M. of eight rats. Within a column. The mean values flowed by a different were significantly different ($p<0.05$) analyzed by Scheffe's test.

TABLE II
EFFECT OF NNFE ON LIPID PROFILE (HIGH-DENSITY LIPOPROTEIN (HDL) AND LOW-DENSITY LIPOPROTEIN (LDL)

Groups	Lipid profile (mg/dl)	
	HDL	LDL
I. Normal controls	52.00±0.63^{c}	14.63±1.51^{a}
II. Diabetic controls	39.67±0.88^{a}	57.87±2.44^{c}
III. Diabetic rats+GB	46.33±1.09^{b}	39.17±2.69^{b}
IV. Diabetic rats+NNFE	50.67±1.01^{bc}	24.97±2.04^{ab}

Data were expressed as mean ± S.E.M. of eight rats. Within a column. The mean values flowed by a different were significantly different ($p<0.05$) analyzed by Scheffe's test.

3.4 Effect of NNFE on Renal Function Test

The renal function including blood urea nitrogen (BUN) and creatinine affected by NNFE was depicted in Table 3.

Table 3, BUN in diabetic controls was significantly ($p<0.05$) increased compared to normal controls. Again, it was reversed in NNFE treated diabetic rats. However, NNFE had no effect on Creatinine. NNFE reduced BUN with a similar potent to GB.

TABLE III
EFFECT OF NNFE ON RENAL FUNCTION TEST (BLOOD UREA NITROGEN (BUN) AND CREATININE (CR)

Groups	Renal function test (mg/dl)	
	BUN	CR
I. Normal controls	31.00±0.45[a]	0.77±0.02[ab]
II. Diabetic controls	39.83±0.17[b]	0.83±0.02[b]
III. Diabetic rats+GB	34.67±0.42[a]	0.82±0.02[b]
IV. Diabetic rats+NNFE	32.00±0.58[a]	0.72±0.02[a]

Data were expressed as mean ± S.E.M. of eight rats. Within a column. The mean values flowed by a different were significantly different ($p<0.05$) analyzed by Scheffe's test.

4 DISCUSSION

The present study was designed to investigate and prove traditional use of flower from Lotus (*N. nucifara*). In addition, its effect on kidney function in animal model of diabetes was carried out. A one of the well known chemical used for induction of diabetes is Streptozotocin (STZ; N-nitrosoderivative of glucose-mine). It is a broad-spectrum antibiotic extracted from *Streptomyces acromogenes* [33] STZ is known to induce not only diabetes but also develop diabetic complication similar to early stage complication of humans. The STZ induced-diabetic rats developed diabetes as indicated by increased fasting blood glucose values and also showed external signs of symptoms. Earlier symptoms of micro vascular complication such as retinopathy, formation of cataract, body weight loss, polyphagia, dried dark coloured stool, neuropathy accompanied with loss in sensation and nephropathy associated with high urine output was observed [34].

Diabetes mellitus is characterized by high levels of blood glucose. In this study, increased in blood glucose level in streptozotocin-induced diabetic ratswas observed. However, the blood glucose level was decreased in diabetic rats treated with NNFE. The present experimental results indicated that ethanolic extract exhibited a potent blood glucose lowering properties in STZ diabetic rats. The possible mechanism by which *N. nucifera* brings about its hypoglycemic action may be stimulating the serum insulin by increasing either the pancreatic secretion of insulin from the β - cells of Islets of Langerhans or its release from bound insulin in line with standard drug (Glibenclamide). The potential role of medicinal plants as hypoglycemic agents has been reported in many studies which supported to ethnobotanical surveys and use of traditional medicines in numerous cultures [35].

Diabetes mellitus is known to cause hyper-lipidemia through various metabolic derange-ments. Among several metabolic derangements, insulin deficiency has been known to stimulate lipolysis in the adipose tissue and gives rise to hyperlipidemia and fatty liver. Thus, in diabetes hypercholesterolemia and hypertriglyceridemia often occurs [2].

In this study, an elevated blood glucose concentration accompanied by increase TC, TG, and LDL but decrease HDL was observed in STZ- induced diabetic rats compared to normal controls. Repeated oral administration of ethanolic NNFE decreased TC, TG and LDL but increased HDL in NNFE treated diabetic rats. These results indicate that NNFE possesses hypolipidemic and hypolipidemic activities by flavonoids from lotus (*Nelumbo nuficera* Gaertn) leaf in diabetic mice showed the dosage of 200 mg/kg is more effective than that of 50 mg/kg. In addition, flavonoids from lotus leaf (FLL) did not exhibit any toxic symptoms in the limited toxicity evaluation in male mice. However, the levels of TC and TG have been decreased significantly in diabetic rats after the FLL supplementation. The FLL supplementation also results to the significant attenuation in the level of serum HDL-c toward the control level which again strengthens the hypolipidemic effect of this extract [36]. There are reports that other medicinal plants have hypoglycemic and hypolipidemic effects that could prevent or be helpful in reducing the complications of lipid profile seen in some cases of diabetes in which hyperglycemia and hypercholesterolemia coexist [37]. The above results suggested that FLL could control blood glucose and modulate the metabolism of glucose and blood lipid [36]. These effects may be due to low activities of cholesterol biosynthesis enzymes and low level of lipolysis which are under the control of insulin [37]. The mechanism on hypolipidemic activity of NNFE may result from stimulating insulin secretion. In-vitro studies with rat hemidiaphragm revealed that the sun-dried flower powder significantly enhanced insulin level. The improvement of glucose tolerance may also be increased peripheral glucose utilisation caused by increase sensitivity of skeletal muscle to endogenous insulin [38].

BUN increased in STZ-induced diabetic rats was decreased in NNFE treated diabetic rats. However, it did not affect on creatinine. These results reveal that the extract is found to exhibits its activity in diabetic nephropathy. It indicates the safety of this plant could be using free from side effect.

Oral administration of ethanolic NNFE on the lvels of blood glucose level give potent antidiabetic effects in rats. The previous study was found that flavonoids can act on hypoglycemic effects and anti-oxidation activities [39] in STZ-induced diabetic rats.

5 CONCLUSIONS

It could be clearly concluded the NNFE had hypoglycemic and hypolipidemic activity. It was non toxic on acute toxicity study and kidney function test. These findings suggest that NNFE at a dosage of 250 mg/kg is a good choice for controlling the blood glucose level in diabetic rats and NNFE is a kind of medicinal plants that can be developed and used as alternatives for diabetic treatment in patients.

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