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Evaluation of Antihyperglycemic and Antihyperlipidemic Potential of *Nelumbo nucifera* Seeds in Diabetic Rats

(Penilaian Potensi Antihiperglisemik dan Antihiperlipidemik Biji *Nelumbo nucifera* dalam Tikus Diabetis)

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ABSTRACT

The present study was aimed at evaluating antihyperglycemic and antihyperlipidemic activity of nuciferin and norcoclaurine constituents of *N. nucifera* seeds, a well-known medicinal plant. The alloxan (100 mg/kg b.w) induced diabetic rats (200-250 g) were divided into seven groups (n = 6). Group I; normal control, Group II; diabetic control, Group III; standard, Group IV-VII were fed with methanolic crude extracts (100, 200 mg/kg), nuciferin and norcoclaurine (10 mg/kg b.w.), received for 15 days in dose dependent manner. The study included different parameters; examination of oral glucose, fasting blood glucose, serum lipid profile and checking for body weight changes. In oral glucose examination, within 60 and 80 min of treatment, extracts, nuciferin and norcoclaurine significantly reduced blood glucose ($p < 0.05$) and restored body weight in diabetic rats. Alloxan- induced diabetic rats showed 30-50% reduction of blood glucose level ($p < 0.05$) and recovered 5-20% body weight at day 15 after ingestion of crude extracts (100-200 mg/kg b.w.); and nuciferin and norcoclaurine (each at 10 mg/kg b.w.). It also recovered significantly elevated biochemical parameters such as triglycerides (TG), low density lipoprotein (LDL), high density lipoprotein (HDL), total cholesterol (TC), serum urea and creatinine. Our findings indicated that *N. nucifera* seeds possess significant antihyperglycemic and antihyperlipidemic activity in diabetic rats.

Keywords: Antihyperglycemic; antihyperlipidemic; norcoclaurine; nuciferin; *N. nucifera*

ABSTRAK

Penyelidikan ini bertujuan untuk menilai aktiviti antihiperglisemik dan antihiperlipidemik jujuk nusiferin dan norkoklaurin biji *N. nucifera*, tumbuhan ubatan yang terkenal. Aloksan (100 mg/kg kW) tikus teraruh diabetis (200-250 g) dibahagikan kepada tujuh Kumpulan (n=6). Kumpulan I; kawalan biasa, Kumpulan II; kawalan diabetis, Kumpulan III; piawai, Kumpulan IV-VII diberi makan dengan ekstrak mentah metanolik (100, 200 mg/kg), nusiferin dan norkoklaurin (10 mg/kg b.w.), menerima dos secara bersandar selama 15 hari. Kajian ini merangkumi parameter yang berbeza; pemeriksaan glukosa secara oral, glukosa darah puasa, profil lipid serum dan pemeriksaan perubahan berat badan. Dalam tempoh 60 dan 80 min rawatan untuk pemeriksaan glukosa secara oral, ekstrak, nusiferin dan norkoklaurin telah mengurangkan glukosa darah ($p < 0.05$) dan memulihkan berat badan tikus diabetis. Aloksan - tikus teraruh diabetis menunjukkan 30-50% pengurangan paras glukosa darah ($p < 0.05$) dan mendapat kembali 5-20% berat badan pada hari ke-15 selepas ketakhadaman ekstrak mentah (100-200 mg/kg b.w.); serta nusiferin dan norkoklaurin (masing-masing pada 10 mg/kg b.w.). Ia juga dengan ketara mendapat kembali peningkatan parameter biokimia seperti trigliserida (TG), lipoprotein ketumpatan rendah (LDL), lipoprotein ketumpatan tinggi (HDL), jumlah kolesterol (TC), serum urea dan kreatinina. Keputusan kajian kami menunjukkan bahawa biji *N. nucifera* mempunyai aktiviti antihiperglisemik dan antihiperlipidemik yang penting dalam tikus diabetis.

Kata kunci: Antihiperglisemik; antihiperlipidemik; norkoklaurin; nusiferin; *N. nucifera*

INTRODUCTION

Diabetes mellitus is known as one of the important causes of morbidity and mortality in the world. The frequency of diabetes according to WHO is about 150 million worldwide and this figure is estimated to increase up to 300 million by the year 2025 (Boyle et al. 2001). Modern medication used for the treatment of diabetes are often associated with side effects (Fowler 2007). Most of the thousand medicinal plants used universally for the traditional treatment of the disease. Antihyperglycemic activity of these plants

was supported by investigational studies (Marlos et al. 1995). However medicinal plants are important and act as alternative therapeutics. It has been shown that medicinal herbs potentially enhanced the immunity against various infections. About thirteen thousand plant species have been observed to have pathological and pharmacological properties (Kumar et al. 2010; Sindhu et al. 2011). The use of herbal remedies were claimed to be more effective and cheaper with minimal side effects (Haldar et al. 2010) than the use of synthetic medicines.

Nelumbo nucifera (*Nelumbonaceae*) is a free floating plant which various parts have been claimed to possess medicinal values. The plant seeds, leaves and roots are taken for the treatment of fever, diarrhea, skin diseases as well as antiseptic and antispasmodics. Dried leaves were applied to sores, rheumatism, lumbago, sciatica and painful tumors. The leaves of this plant also act as analgesic, anesthetic, expectorant, vermifuge and sedative. The juice of leaves is used in ophthalmia, earache, toothache to relieve pains in gout, inflammation and leprosy (Sridhar et al. 2007). *N. nucifera* is used in the prevention of miscarriages and as an antihemorrhagic agent especially for excess menstrual bleeding (Huang et al. 2010). In this study, we investigated the antihyperglycemic and antihyperlipidemic activity of *Nelumbo nucifera* constituents in diabetic rats.

MATERIALS AND METHODS

PLANT MATERIAL

Mature and fully dried seeds of *Nelumbo nucifera* were obtained from a local supplier (public market) in Bannu city. Further taxonomic identification was made by Prof. Abdur Rehman, Govt. Post Graduate College Bannu, KPK, Pakistan. A specimen (BG-201) has been submitted at the University of Science and Technology, Bannu, KPK Pakistan herbarium.

EXTRACTION AND ISOLATION OF COMPOUNDS

N. nucifera seeds (8 kg) were refluxed with MeOH and evaporated to yield gummy residue (400 g). The crude methanolic extract was suspended in water and pooled with 0.5 N H₂SO₄ (pH1.5) followed by extraction with CHCl₃ (3 × 2 L) to afford acidic and non-acidic mixtures. The acidic aqueous solution was basified (pH8-10) by 10% KOH (aq) and extracted with CHCl₃ to yield 15 g of alkaloidal mixture (NA). NA was fractionated on silica gel column with elution of n-hexane, EtOAc and MeOH solvent mixtures. The resulted fractions (NA1-NA9) were put into repeated flash column chromatography using solvent system n-hexane: acetone: diethyl amine (9:1: 2 drops) to furnish nuciferin (**1**) and norcoclaurine (**2**), respectively (Figure 3).

CHARACTERIZATION OF COMPOUNDS

Infrared (IR) spectra were recorded on a SHIMADZU-FTIR 8101 M spectrophotometer using KBr discs. For nuclear magnetic resonance (NMR), ¹H and ¹³C, Distortionless Enhancement by Polarization Transfer (DEPT) and Heteronuclear Single Quantum Coherence (HSQC) NMR spectra were recorded on Bruker Avance 400 MHz. The chemical shift (δ) values are given in parts per million (ppm) with coupling constant *J* in Hertz. Electron impact mass spectra (EI-MS) were recorded on a HP5989B mass spectrometer. Thin layer chromatography was carried out on pre coated silicagel GF₂₅₄ (Merck, Germany) and spots were

sprayed with dragendorff's reagent. Flash chromatography was performed using silica gel 70-230 mesh (Merck).

Nuciferin Colourless solid; mp 240-242°C, M.F=C₁₉H₂₁NO₂, EI-MS (*m/z*), [M]⁺ 295.1530. The data was in complete agreement with that for nuciferin (Ma et al. 2014).

Norcoclaurine (1) Colourless prisms; mp 239-242°C, M.F=C₁₆H₁₇NO₃, EI-MS (*m/z*), [M]⁺ 269.1392. The data was in close resemblance with that for norcoclaurine in literature (Mukherjee et al. 2009).

CHEMICALS

Glucometer (Roche Diagnostics Corporation, USA). Glibenclamide and Alloxan monohydrate (Sigma Germany). Methanol (Merck). Sodium citrate buffer.

ANIMALS

Forty two adult Sprague dawley strains of albino rats (200-250 g, b.w.) were provided by the National Institute of Health, Islamabad. The animals were maintained at a constant temperature (24±1°C) on a 12 h light/dark cycle with free access to food and water. Before starting the experiment, the animals went through an adjustment period of 20 days.

EXPERIMENTAL INDUCTION OF DIABETES

Diabetes was induced in the experimental animals by the intraperitoneal injection of alloxan monohydrate (100 mg/kg). Alloxan treated rats received 5% glucose instead of water for 28 h after diabetes induction in order to reduce death due to hyperglycemic shock. Glucose levels were measured with a portable glucometer. Only animals with fasting glycemia over 300 mg/dL in blood were considered diabetic and used for the study. The Ethical Committee of Quaid-e-Azam University approved the study protocol for animal care and feed (Nagappa et al. 2003).

EXPERIMENTAL DETAILS

Afterwards, the rats were divided into seven groups comprising of six animals in each group. Groups I and II were normal and diabetic control, group III was standard, treated with Glibenclamide (10 mg/kg). Groups IV, V, VI and VII were treated with nuciferin, norcoclaurine (10 mg/kg) and *N. nucifera* methanolic extract (100-200 mg/kg), respectively. After 15 days, rats were anesthetized and samples were collected for different analyses. For the estimation of glucose level in blood and urine, samples were collected at days 0, 5, 10 and 15 after treatment with plant extract.

The level of blood glucose was measured by glucometer and the results were compared with standard glibenclamide treated group III. For the estimation of biochemical parameters blood was collected from retro orbital of each rat

and centrifuged at 4000 rpm for 10 min. TG, HDL, LDL, TC, urea, alkaline phosphate, creatinine and total protein were measured by an auto analyzer (Dash et al. 2005; Sharma et al. 1997).

STATISTICAL ANALYSIS

Values are expressed as mean \pm S.E.M. Data were determined statistically significant using student's t-test. P values of less than 0.01 and 0.05 were taken as significant.

RESULTS

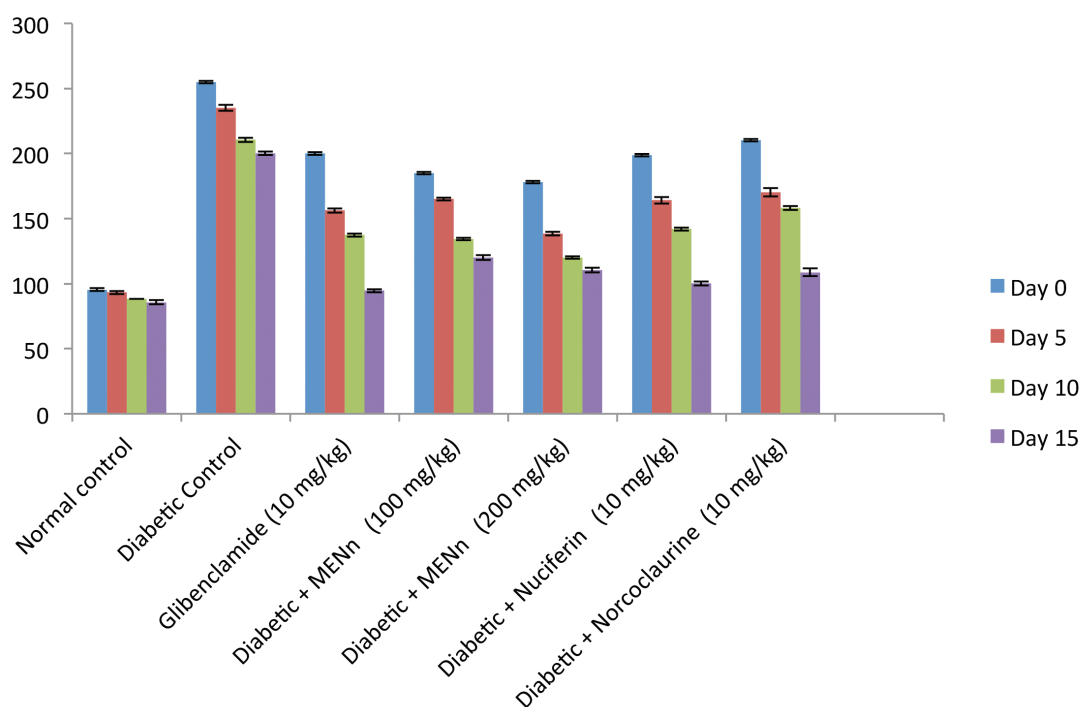
The effects of nuciferin, norcoclaurine (10 mg/kg body weight/day) and *Nelumbo nucifera* methanolic extracts

(MENn) (100-200 mg/kg body weight /day) on blood glucose level in alloxan induced diabetic rats are illustrated in Table 1 and Figure 1. A marked rise in blood glucose level was observed in diabetic group (200.25 \pm 1.32 mg/dL), as compared to normal group (85.65 \pm 1.53 mg/dL), of animals at 15th day. The standard glibenclamide (94.55 \pm 1.20 mg/dL) and nuciferin (100.10 \pm 1.45 mg/dL), norcoclaurine (108.80 \pm 3.15 mg/dL) as well as *Nelumbo nucifera* methanolic extracts (110.45 \pm 1.79 mg/dL) significantly decreased the glucose level as compared to diabetic group ($p < 0.05$) (Table 1). Hence, findings from this study showed that there is a reduction in glucose level but the level did not return to that in normal control. There is marked reduction in 15 days.

TABLE. 1 Effect of *Nelumbo nucifera* on blood glucose level in diabetic rats

Treatment	Blood glucose level(mg/dL)			
	Day0	Day5	Day10	Day15
Normal control	95.41 \pm 1.65*	93.27 \pm 1.25	88.32 \pm 0.12	85.65 \pm 1.53
Diabetic Control	255.00 \pm 2.85*	235.22 \pm 2.32*	210.55 \pm 1.68*	200.25 \pm 1.32*
Glibenclamide (10 mg/kg)	200.01 \pm 1.85	156.27 \pm 1.68	137.36 \pm 1.20	94.55 \pm 1.20*
Diabetic + MENn (100 mg/kg)	185.10 \pm 2.85	165.09 \pm 1.08	134.33 \pm 1.03*	120.01 \pm 1.9*
Diabetic + MENn (200 mg/kg)	178.00 \pm 1.35	138.5 \pm 1.55*	120.17 \pm 0.97*	110.45 \pm 1.79*
Diabetic + Nuciferin (10 mg/kg)	198.70 \pm 3.85	164.10 \pm 2.51	142.00 \pm 1.23	100.10 \pm 1.45
Diabetic + Norcoclaurine (10 mg/kg)	210.20 \pm 4.67	170.20 \pm 3.25	158.11 \pm 1.43	108.80 \pm 3.15

Each value is \pm SEM of 5 animals * $p < 0.05$: Normal control vs diabetic control; Diabetic control vs treated groups



Each Value is \pm SEM of 5 animals * $p < 0.05$: Normal control vs diabetic control; Diabetic control vs treated groups. Significant decrease was reported as on 15th day by the methanolic extracts 100-1000 mg/kg as compare to standard drug

FIGURE 1. Effect of *Nelumbo nucifera* on blood glucose level in diabetic rats

The effect of nuciferin, norcoclaurine (10 mg/kg) and methanolic extract (MENn) (100-200 mg/kg) on body weight is summarized in Table 2 and Figure 2. The body weight of normal rats was observed to be stable (180.25±1.53 g) whereas decrease in weight was observed in diabetic rats (148.25±2.52 g). However, the diabetic group treated for 15 day with nuciferin (181.120±3.14 g), norcoclaurine (177.92±1.42 g) and methanolic extract (MENn) (178.45±2.79 g) showed significant increase in body weight ($p<0.05$). The body weight was significantly recovered 5-10% when examined on 15th day at 100-200 mg/kg ($p<0.05$). Marked increase in weight was observed in the standard glibenclamide group (14.9%).

Table 3 describes the effect of methanolic extract on serum profile. Extracts significantly reversed hyperlipidemia in diabetic animals as compared to normal. A gradual decrease in total cholesterol, low density protein (LDL), serum urea, alkaline phosphate, creatinine, triglycerides and increase in HDL and serum protein was observed in methanolic extract and standard groups. Marked significant

results was seen using nuciferin and norcoclaurine. Doses of 100-200 mg/kg also showed reverse in biochemical parameters but not significantly. The main symptom of diabetes is frequent and excess production of urine. High amount of urine glucose was found in diabetic control while treated groups contained no or little glucose in urine. No glucose was found in normal control group.

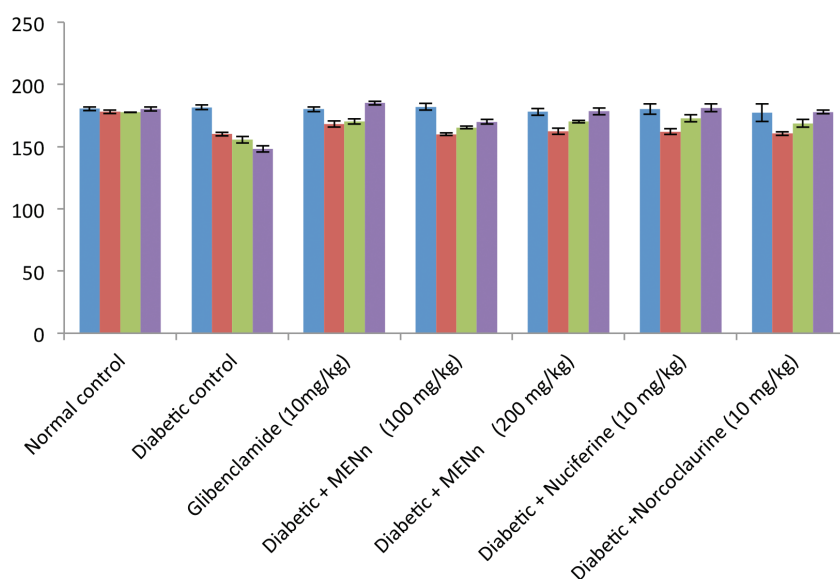
DISCUSSION

The present study is a preliminary assessment of the antidiabetic, antihyperglycemic and antihyperlipidemic activity of *N. nucifera* methanolic constituents. Alloxan, a highly reactive substance causes a rapid destruction of β cells of Langerhans and thus rapidly raises blood sugar inducing hyperglycemia. This study suggests that nuciferin, norcoclaurine are both potent at reducing glucose levels as well as in recovering body weight. Administration of the methanolic extract (100-200 mg/kg b.w.), nuciferin and norcoclaurine (10 mg/kg)

TABLE 2. Effect of *Nelumbo nucifera* extract on body weight in diabetic rats

Treatment	Body weight variation (G)			
	Day0	Day5	Day10	Day15
Normal Control	180.54±1.55	178.01±1.35	177.62±0.12	180.25±1.53
Diabetic Control	181.58±1.85*	160.22±1.52*	155.55±2.58*	148.25±2.52*
Glibenclamide (10 mg/kg)	180.01±1.90	168.27±2.48	170.25±2.17*	185.05±1.50*
Diabetic + MENn (100 mg/kg)	182.10±2.85	160.00±1.08	165.33±1.03*	170.01±1.90*
Diabetic + MENn (200 mg/kg)	178.00±2.75	162.50±2.55	170.17±0.97*	178.45±2.79*
Diabetic + Nuciferin (10 mg/kg)	180.21±4.23	162.130±2.31	172.80±2.75	181.120±3.14
Diabetic + Norcoclaurine (10 mg/kg)	177.33±3.12	160.51±1.43	168.71±3.11	177.92±1.42

Each value is \pm SEM of 5 animals * $p<0.05$: Normal control vs diabetic control; Diabetic control vs treated groups



Each Value is \pm SEM of 5 animals * $p<0.05$: Normal control vs diabetic control; Diabetic control vs treated groups. Body weight was significantly recovered 5-10% on 15th day at 100-1000 mg/kg

FIGURE 2. Effect of *Nelumbo nucifera* on body weight in diabetic rats

significantly reduced the fasting glucose level of blood in alloxan induced diabetic rats as compared to normal control. The decline in the body weight observed in the diabetic control group may be due to increase uptake of muscle glucose. The decline in the body weight observed in the diabetic control group was also reported to be recovered. However, administration of the antidiabetic plant extracts resulted in prevention of tissue loss and body weight (Szkudelski 2001; Yadav et al. 2000).

Alloxan-induced diabetes in rats resulted in weight loss due to protein and muscle wasting (Chatterjea & Shinde 2002). *N. nucifera* enhanced body weight of diabetic rats in our study due to improvement in metabolic activity and maintained normal glucose level. The difference in body weights during the treatment with *N. nucifera* were less as compared to the diabetic control. The weight improvement is due to glycemic control which may be another probable way of antidiabetic action (Maiti et al. 2004).

Elevated plasma triglycerides, low HDL, total cholesterol and increased concentration of low LDL causes hyperglycemia. The high level of cholesterol and triglyceride levels decreased the level of HDL and increased the concentration of small dense LDL by

lipoprotein lipase activation and lecithin acyl-cholesterol transferase (Mooradian 2009; Mooradian et al. 2008). In the present study, high level of serum TC, TG, LDL and decreased HDL cholesterol concentration in alloxan-induced diabetic mice are in accordance with the previous research findings (Howard 1987). However, treatment with *N. nucifera* seed extract normalized all the lipid profile parameters.

Various metabolic alterations occurred in animals due to insulin deficiency and thus increased blood glucose level, cholesterol level, triglycerides (TG), total protein, urine sugar and alkaline phosphate and transaminase. Low dose of alloxan (100 mg/kg (b.w.)) causes destruction of β cells and even causes permanent diabetes in animals. Regeneration is possible in such animals due to surviving β cells (Ayber et al. 2008; Prince et al. 2000).

The major causes of cardiovascular disease in diabetic patient are abnormalities in lipid profile. Glycemic control is an ideal treatment in controlling diabetes. Major coronary risk factors are high level of total cholesterol and LDL (Temme et al. 2001). In order to prevent cardiac diseases, it was necessary to measure biochemical parameters. In this study, *N. nucifera* methanolic extracts showed significant reduction in TC,

TABLE 3. Effect of *Nelumbo nucifera* extract on serum profile in diabetic rats

Parameters	Normal Control	Diabetic control	Glibenclamide (10 mg/kg)	Diabetic + MENn (100 mg/kg)	Diabetic + MENn (200 mg/kg)	Diabetic + Nuciferin (10 mg/kg)	Diabetic + Norcoclaurine (10 mg/kg)
Serum urea (mg/dl)	25.91±0.25	50.25±5.23*	33.01±2.25*	30.27±2.50	31.00±2.15	28.52±1.28*	30.55±2.50*
Serum creatinine (mg/dl)	0.85±0.09	2.36±0.1	1.46±0.06	0.42±0.02	1.21±0.05	1.25±0.07*	1.33±0.08*
TC (mg/dl)	51.55±1.09	90.65±1.02*	55.25±1.08*	80.03±1.25	75.19±1.20	60.00±1.10*	57.65±1.03
TG (mg/dl)	84.56±1.01	130.42±1.24	100.46±1.06	120.88±1.15*	109.05±1.04*	104.01±1.12	98.04±1.02*
LDL (mg/dl)	20.45±1.87	58.78±0.62*	23.89±1.35	40.84±1.20	34.23±0.68*	30.73±0.02	25.29±1.54
HDL (mg/dl)	32.5±1.6	28.2±1.2	65.3±1.8*	45.0±1.6*	53.3±1.7*	55.2±1.9*	60.5±1.1*
Plasma Protein (g/dl)	8.11±0.5	6.7±0.01*	7.2±0.4	8.00±0.5	6.90±0.2	6.8±0.1	7.9±0.3
Urine sugar	Nil	++	Nil	+	+	Nil	Nil
Alkaline phosphatase (U/L)	120.2±4.0	385±5.6*	125.1±3.7*	165±10.5	162.8±7.2	155.6±6.01	140.03±4.6*

Each Value is \pm SEM of 6 animals * $p < 0.05$ - Normal control vs diabetic control; Diabetic control vs extract groups

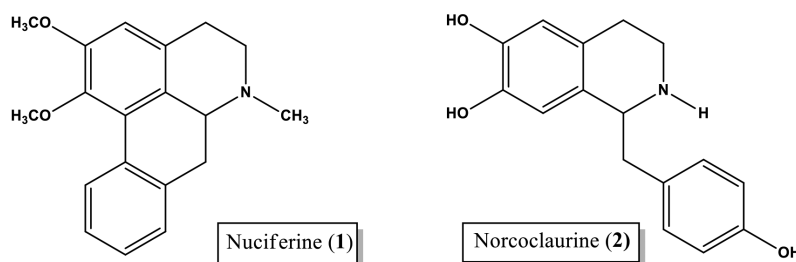


FIGURE 3. Nuciferin (1) and norcoclaurine (2) isolated from the seeds of *N. nucifera*

TG, LDL, creatinine, alkaline phosphate and urine sugar, serum urea levels and high level of HDL and serum protein in diabetic rats. However, the elevated HDL and serum protein level observed using *N. nucifera* was comparable to the standard drug Glibenclamide. Therefore *N. nucifera* is potentially useful in the prevention of atherosclerosis and heart disease (Leontowicz et al. 2002).

CONCLUSION

It was concluded from the results obtained that nuciferin, norcochlorogenic acid and crude methanolic extract from *N. nucifera* seeds has dose dependent effect with higher doses showing significant antidiabetic activity and decreased elevated blood glucose, cholesterol, triglycerides and thereby increasing the high density lipoprotein (HDL) levels in diabetic rats, hence possess significant antihyperglycemic properties in alloxan-induced diabetic rats. *N. nucifera* may be potentially effective against diabetes mellitus. Further investigation on this medicinal plant is recommended to exploit its hidden medicinal values. The authors declare no conflict of interest.

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