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International Journal of Pharmaceutical Research & Allied Sciences, 2016, 5(1): 34-39

Research Article

ISSN : 2277-3657
CODEN(USA) : IJPRPM

Hypoglycaemic and Antihyperglycaemic Activities of an Aqueous Leaf Extract of *Adenanthera Pavonina* (Fabaceae) In Rats

D. M. R. K. Dissanayake*[a], M. D. J. Wijayabandara[b,c] and W. D. Ratnasooriya[d,e]

[a]*Department of Chemistry, Faculty of Science, University of Colombo, Sri Lanka*
[b]*Department of Pharmacy, Faculty of Medicine, University of Colombo, Sri Lanka*
[c]*Pharmacy Unit, Faculty of Medical Sciences, University of Sri Jayewardenepura, Sri Lanka*
[d]*Department of Zoology, Faculty of Science, University of Colombo, Sri Lanka*
[e]*Department of Basic Sciences, Faculty of Allied Health Sciences, Sir John Kotelawala Defense University, Sri Lanka,*
E-mail: ranga@chem.cmb.ac.lk
Subject: Pharmacology

ABSTRACT

According to the Sri Lankan folk medicine, hot water extract (HWE) of mature leaves of Adenanthera pavonina (Family; Fabaceae) is claimed to possess blood glucose lowering potentials. However, this claim is not scientifically proven or refused. As such, this study investigated the glycaemic regulatory properties of HWE of A. pavonina mature leaves using rats. Different doses of HWE (500, 750 and 1000 mg/kg) or 1 ml distilled water (negative control) or 22.5 mg/kg of tolbutamide (positive control) were orally administrated to normoglycaemic rats and their fasting (n=6 per group), random (n=6 per group) and post parenial (n=6 per group) (after a 5 ml/kg 50% oral glucose challenge) serum glucose levels were determined at hourly intervals for 4 h using standard procedures. The results showed, for the first time, that HWE of A. pavonina leaves possesses significant ($P < 0.05$) hypoglycaemic effects in both fasted (all 3 doses, up to 2 h) and fed (only mid dose tested, up to 2 h) rats, and antihyperglycaemic effect (all doses, up to 3 h following glucose challenge). Except for the production of watery stools the sub chronic (21 days) administration of HWE of A. pavonina leaves was well tolerated with no hepatotoxic (in terms of SGOT and SGPT levels), nephrotoxic (in terms of serum creatinine and urea levels) or neurotoxic (in terms of reaction time of bar and bridge tests) effects. It is concluded that HWE of A. pavonina leaves exhibit safe oral hypoglycaemic and antihyperglycaemic activities supporting its use in Sri Lankan folk medicine in the treatment for diabetic conditions.

Key words: *Adenanthera pavonina leaves, diabetes, antihyperglycaemia, hypoglycaemia, Sri Lanka.*

INTRODUCTION

Diabetes mellitus is a chronic metabolic disease, marked by high levels of glucose in blood. It causes the elevation of fasting blood glucose which occurs due to relative or absolute deficiency in insulin or reduction of insulin sensitivity.[1,2] Today, this is a very common disease. Currently, there are over 370 million diabetic patients worldwide and this is likely to increase to 590 million or more by 2035.[3,4] Therefor, it is an urgent need for investigation and development of novel therapeutically active anti-diabetic agents, mainly from natural/herbal sources and there are over 50% of all modern clinically used drugs have either natural (based on Ayurveda, traditional and folk medicine) or semisynthetic origin.[5] The demand for herbal product has been increasing globally at an annual rate of 8%; and the estimated value of the global herbal market would be US $5 trillion by 2050.[6]

Fascinatingly, today about 1500 species of medicinal plants are used in Sri Lanka, among them around 208 plants are frequently used as Ayurveda or traditional preparations.[7,8] *Adenanthera pavonina* (L.) (Family: Fabaceae, subfamily: Mimosoideae, Sinhala: Madatiya, Tamil: Tilam and Manjadi, Sanskrit: Kusandana) has long been an important tree currently found in South Asian counties including Sri Lanka, Southeast Asian counties, the Pacific Islands, China, Malaysia, Western and Eastern African counties and most island nations of both the Pacific and the Caribbean. Seeds of *A. pavonina* are used as poultice and powdered seeds are externally applied for hastening suppuration, treatment for boils and in inflammation. Seeds are edible but toxic. It is also useful in cholera and general paralysis. [9,10] Decoctions of leaves and bark are used as a remedy for chronic rheumatism, gout, haematuria, haematemesis and intestinal hemorrhage. Furthermore, the leaves and the bark are used as a remedy for sprains and snake bite. Leaves are also used as atonic and as an astringent used to suppress diarrhea and dysentery. Roots are used as emetic and purgative.[11]

Many people, specially, in Sri Lanka believe that the leaf of this plant possesses glucose lowering activity and the evidence from folk medical usage also suggest this effect.[12] However, this claim is not scientifically proven or refused. The aim of this study was to scientifically evaluate the glucose lowering potential of an aqueous extract of the leaves of *A. pavonina* using rats. In addition the safety profile of the aqueous leaf extract of *A. pavonina* was evaluated using normoglycaemic rats.

MATERIALS AND METHODS

Plant material

The fresh leaves of *A. pavonina* were collected (3.1 kg) from a matured tree located at the Faculty of Science, University of Colombo, Sri Lanka, in November, 2010. The leaves were washed under running tap water, air dried for 24 hours and subsequently oven dried for one week at 40^0C (1.2 kg). These dried leaves was powdered and refluxed for one hour by mixing with distilled water. The aqueous extract was freeze dried (180 g) and stored in air tied bottle at 4^0C until the required dosages were made for oral administration. The appropriate weight of the freeze dried powder was dissolved in distilled water to obtain the required dosage of Hot Water Extract (HWE) of the leaves of *A. pavonina* 30 min before administration to rats.

Experimental animals

Healthy, adult male and female, Sprague - Dawley rats weighing 200 – 250 g were used in this study. The animals were kept in plastic cages (5 per cage) in the animal house Faculty of Medicine, University of Colombo, Sri Lanka, under standard conditions (temperature: 28-31^{0}C, photoperiod: approximately 12 h natural light per day, relative humidity: 50-55%). The animals were fed with pelleted food and tap water; except at the time of experimental procedure. The animals were handled only during cage cleaning. All the experiments were conducted in accordance with the internationally accepted laboratory animal use and care (based on Helsinki convention), and the guidelines and the rules of Ethics Review Committee of the Faculty of Medicine, University of Colombo for animal experimentation.[13] Ethical clearance was obtained from ethics committee (2011) , Faculty of Medicine, University of Colombo, Sri Lanka (Ethical clearance serial number: EC-11-026)

Evaluation of serum glucose level

Fasting serum glucose level (FSG)

Thirty rats were fasted over night for 16 h, but water was allowed *ad libitum*. Under aseptic precautions, using light ether anaesthesia, 0.5 ml of blood was obtained from their tails. Serum was separated and their glucose concentration was determined using glucose assay kit (Randox assay kit, Randox Laboratories Ltd., County Antrim, United Kingdom) and spectrophotometer (STD 1100, Billerica, MA, United States of America). These rats were then randomly divided into five groups (n=6 per group) and treated orally in the following manner:

Group 1: Administered with 1000 mg/kg of HWE
Group 2: Administered with 750 mg/kg of HWE
Group 3: Administered with 500 mg/kg of HWE
Group 4: Administered with 22.5 mg/kg of tolbutamide (positive control)
Group 5: Administered with 1 ml of distilled water (negative control)

Serum glucose levels were measured at hourly intervals for 4 h. [14,15]

Random serum glucose level (RSG)

Twelve rats were randomly divided into two equal groups (n=6 per group), and treated orally in the following manner

Group 1: Administered with 750 mg/kg of HWE
Group 2: Administered with 1 ml of distilled water (negative control)

Blood samples were collected from tail, 1 h prior to commencement of the treatment and at hourly intervals for 4h. Serum glucose levels were measured as mentioned under FBG. [14,15]

Oral glucose tolerance test (OGTT)

To ascertain the effect of HWE of *A. pavonina* leaves during acute glycaemia, a glucose tolerance test was performed. Thirty rats were fasted for 16 h and randomly assigned into five groups (n=6 per group). These rats were orally treated in the following manner

Group 1: Administered with 1000 mg/kg of HWE
Group 2: Administered with 750 mg/kg of HWE
Group 3: Administered with 500 mg/kg of HWE
Group 4: Administered with 22.5 mg/kg tolbutamide (positive control)
Group 5: Administered with 1 ml of distilled water (negative control) One hour later, all these rats were orally loaded with 5 ml/kg of 50% (w/v) glucose solution. Blood samples were collected from the tails of these rats immediately prior to administration of oral glucose challenge and hourly intervals for 4h after glucose administration.[14,15,16,17,18]

Toxicological study

The toxicological study was based on neurotoxicity (Bar test and Bridge test), Hepatotoxicity (SGOT and SGPT levels) and Renal toxicity (serum creatinine and urea levels). Then, the treated rats were observed for overt sign of acute toxicity such as salivation, yellowing of hair, loss of hair, postural abnormalities, behavioral changes, fur erection, exophthalmia and aversive behavior. In order to investigate acute toxicity twelve healthy rats were randomly divide into two groups. One group was treated as a control group and another group was treated as test group. The test group was treated with 750 mg/kg of HWE daily for 21 consecutive days and the control group was similarly treated with 2 ml of distilled water. On day 1 pretreatment and day 1 post treatment (Treatment period being 21 consecutive days) the following toxicological tests were performed.

Evaluation of Neurotoxicity

Bar test: A HWE treated rat or a control rat was kept on a rotating bar with 12 rotate/min and the time taken to fall from the bar (the reaction time) was recorded. This procedure was done for all treated and control rats.

Bridge test: A HWE treated or a control rat was hanged on a horizontal bar from its fore limbs. Time taken to fell from the bar (the reaction time) was recorded. This procedure was done for all treated and control rats.

Evaluation of Hepatotoxicity and Renal toxicity

Blood was collected from tail using aseptic precautions from 6 HWE treated and 6 control rats one day before treatment and one day after post treatment.(Treatment period being 21 consecutive days). Serum separated and SGPT, SGOT, serum creatinine and urea levels were measured using assay kits (Randox assay kit, Randox Laboratories Ltd., County Antrim, United Kingdom) according to the manufacturer's instructions.

Determination of body weight

Body weights were determined on the rats used in section 2.5 using an electronic balance (MP600, Chyo Corp. Ltd, Tokyo, Japan) one day prior to treatment and one day after post treatment (Treatment period being 21 consecutive days). [19,20]

Statistical analysis

Data are expressed as the mean ± standard error of mean (SEM). Statistical analysis was performed using ANOVA for hypoglycemic test and Mann-Whitney U test for toxicological study. Significant values were set at $P \leq 0.05$. Microsoft Excel 2007 & Minitab 14 were the software used in the analysis of data.

RESULTS

Effect on fasting serum glucose level

The results are summarized in Table 1. As shown, intermediate and high doses of the HWE reduced the serum glucose level significantly ($P < 0.05$) at the 1st hour(intermediate dose: by 18%, high dose: by 17%), 2nd hour (intermediate dose: by 19%, high dose: by 15%) and 3rd hour (intermediate dose: by 15%, high dose: by 16%) following oral administration of the HWE. Tolbutamide, the reference drug also significantly ($P \leq 0.05$) reduced the serum glucose level. (1st hour: by 30%, 2nd hour: by 34% and 3rd hour: by 30%).

Effect on random serum glucose level

The results are summarized in Table 2. As shown, intermediate dose of the HWE reduced the serum glucose level significantly ($P < 0.05$) at the 1st hour (by 9%) and 2nd hour (by 8%) following oral administration of the extract.

Table 1: Effects of oral administration of Hot Water Extract (HWE) of the leaves *A. pavanina* [doses; 500, 750, 1000 mg/kg] reference drug (tolbutamide) and control (distilled water) on the fasting serum glucose levels of rats. (mean ± SEM)

Treatment	Dose mg/kg	Fasting Serum Glucose Levels (mg/dL)				
		Pre-treatment	Post treatment			
			1st hour	2nd hour	3rd hour	4th hour
Low dose	500.0	79.83 ± 3.93	75.50 ± 2.95	76.50 ± 3.86	77.33 ± 5.92	80.00 ± 5.09
Int. dose	750.0	83.33 ± 1.96	68.17 ± 1.30*	68.17 ± 4.17*	69.50±5.51*	75.00± 5.78
High dose	1000.0	79.83 ± 3.19	69.33 ± 4.38*	71.00 ± 5.09	68.83±4.11*	79.17 ± 3.52
Reference drug (Tolbutamide)	22.5	82.67 ± 1.36	58.33 ± 2.29*	55.50 ± 2.13*	57.50±1.38*	61.00±1.53*
Control	D.W.	79.83 ±3.70	83.17 ± 3.35	83.67 ± 2.20	82.00 ± 2.09	76.33 ± 3.17

*Values are significant at * P< 0.05 compared with the respective controls ;*

Table 2: Effects of oral administration of Hot Water Extract (HWE) of the leaves *A. pavanina* [dose;750 mg/kg] and distilled water/DW (control) on the random blood glucose levels of rats. (mean ± SEM)

Treatment	Dose mg/kg	Random Blood Glucose Levels (mg/dL)				
		Pre-treatment	Post treatment			
			1st hour	2nd hour	3rd hour	4th hour
Intermediate dose	750	127.33±5.09	123.33±4.13*	124.83±4.12*	125.50±2.69	121.50± 3.42
Control	DW	133.17±2.89	135.83±2.98	135.33±3.27	129.50±1.89	126.67±1.99

*Values are significant at * P < 0.05 compared with the respective control;*

Table 3: Effects of oral administration of Hot Water Extract (HWE) of the leaves *A. pavanina* [doses; 500, 750, 1000 mg/kg, reference drug (tolbutamide) and distilled water/DW (control) on the oral glucose tolerance test of rats. (mean ± SEM)

Treatment	Dose mg/kg	Oral Glucose Tolerance Test (mg/dL)				
		Pre-treatment	Post treatment			
			1st hour	2nd hour	3rd hour	4th hour
Low dose	500.0	80.67 ± 2.20	102.33±2.99*	96.33 ± 2.91*	85.83 ±3.59*	86.00 ± 2.28
Intermediate dose	750.0	87.50 ± 3.73	101.17± 3.84*	82.50 ± 3.20*	86.67± 2.04*	93.00±3.27
High dose	1000.0	84.17± 3.07	105.83± 2.68*	100.67± 1.98*	90.67± 2.18*	91.67± 2.11
Ref. drug	22.5	88.83± 3.72	72.50± 3.56*	70.33± 1.65*	73.67±1.78*	84.00± 2.37*
Control	D.W.	88.17± 2.47	122.67± 4.29	113.50± 2.51	105.83± 2.79	97.00± 2.19

*Values are significant at * P < 0.05 compared with the respective controls ;*

Effect on oral glucose tolerance test

The results are summarized in Table 03. As shown, all three doses of HWE significantly ($P < 0.05$) reduced the raising of serum glucose level following glucose challenge at 1st hour (low dose: by 17%, intermediate dose: by 18%, high dose: by 14%), 2nd hour (low dose: by 15%, intermediate dose: by 27%, high dose: by 12%) and 3rd hour (low dose: by 19%, intermediate dose: by 18%, high dose: by 14%) following oral administration of the extract with compare to the positive control (1st hour: by 41% and 3rd hour: by 30%).

Effect on Neurotoxicity

The reaction times of bar and Bridge tests showed that there was no significant difference ($P > 0.05$) in reaction time following 21 days of oral treatment with the intermediate dose.[(bar test; pre tratment: control vs treatment, 52.50±2.51 vs 53.33±1.36 s, post treatment: control vs treatment, 67.50±2.25 vs 71.67±1.54 s), (Bridge test pre tratment: control vs treatment, 35.00±1.29 vs 32.50±1.38, post treatment: control vs treatment, 37.50±3.35 s vs 35.88±3.00 s)]

Effect on Hepatotoxicity and Renal/nephro toxicity

The results of SGOT, SGPT, serum urea and serum creatinene levels indicated that there was no significant difference ($P > 0.05$) following 21 days of oral treatment with the intermediate dose. [(SGOT test; pre tratment: control vs treatment, 45.16±0.75 IU/L vs 45.71±1.98, post treatment: control vs treatment, 44.76±1.62 vs 44.61±1.72), (SGPT test, pre tratment: control vs treatment, 37.70±1.75 IU/L vs 38.50±0.98, post treatment: control vs treatment, 37.37±1.29 vs 36.93±0.07), (serum urea level, pre tratment: control vs treatment, 48.13±0.44 mg/dL vs 48.95±0.20, post treatment: control vs treatment, 33.17±1.38 vs 33.83±1.35), (creatinene test, pre tratment: control vs treatment, 0.783±0.024 mg/dL vs 0.816±0.012, post treatment: control vs treatment, 0.733±0.045 vs 0.883±0.040)]

Body weight

21 days of oral treatment of HWE did not significantly ($P > 0.05$) alter the body weight of the tested rats. (pre tratment: control vs treatment, 251.33±1.75 g vs 245.50±0.98, post treatment: control vs treatment, 251.00±2.11 vs 248.16±0.73)

DISCUSSION

This study examined the blood glucose regulating properties of *A. pavonina* mature leaves using oral administration and rats with a view to extrapolate the data obtained to humans. Rat is a well-recognized animal model for investigation of glycaemic regulatory properties of both natural and synthetic agents.[21]

The results clearly showed, for the first time, that hot water extract of *A. pavonina* leaves possess both hypoglycaemic and antihyperglycaemic activities. Hypoglycaemic activity was evident in fasting (percentage reduction: 18%), as well as in fed rats (percentage reduction: 9%), but was more pronounced in fasting rats. The onset of the hypoglyceamic effect was rapid (within one hour) and had a short duration of action (up to 3 hour on fasting rats and up to 2 hour in fed rats). This suggest quick absorption of the active ingredient(s) from the gastrointestinal tract and/or rapid breakdown of it in the liver (high first past metabolism) and/or fast removal of it though the kidneys (high renal clearance). The hypoglycaemic effect of *A. pavonina* leaf extract was not dose related and inferior to the reference antidiabetic drug, tolbutamide (by 0.6 fold). Having a moderate hypoglycaemic effect, as seen in this study, is advantages in one sense as it would not induce unpleasant side effect such as hypoglycaemia, disturbance in liver function, lactic acidosis, anorexia, nausea and weight loss as reported with some currently available oral antidiabetic therapeutics.[22] In the oral glucose tolerance test, all the three doses of *A. pavonina* leaf extract significantly inhibited the rise in blood glucose level. This strongly indicates that the extract has insulin releasing potentiation activity by acting on beta cell of the pancreas as reported with sulphonyl ureal antideabetic drugs.[22,23] A previous study on phytochemical screening of the leaves of A. pavonina has shown that it contains oleanolic acid. Interestingly, there is evidence that oleanolic acid can potentiate insulin release. [24,25,26] Alternatively, an inhibition in the raise of blood glucose level following glucose challenge may indicates an insulinomimetic action of the *A. pavonina* leaf extract as reported with some herbal agents.[27] In complete contrast, such as an improvement in the oral glucose tolerance test may result from an increase in insulin sensitivity of glucose receptors. Further studies are obviously needed to pinpoint the exact mode of action.

Sub chronic oral administration of the extract did not alter the body weight. Further, it was neither hepatotoxic (in terms of SGOT and SGPT levels) nor nephrotoxic (in terms of serum creatinine and serum urea levels) nor neurotoxic (in terms of reaction times in bar and Bridge tests). In addition, it did not induce any overt signs of toxicity such as salivation, yellowing of hair, loss of hair, postural abnormalities, behavioral change, fur erection, exophthalmia or aversive behavior. However, HWE created mild diarrhea. Diarrhea is reported with some biguanide antidiabetis drugs such as metformin.[22,23]

CONCLUSION

In conclusion, this study showed, for the first time, that the aqueous hot water extract of mature leaves of A. pavonina possess safe oral hyperglycaemic and antihyperglycaemic activities. Furthermore, the study scientifically justified the Sri Lankan folk claim that leaf extract of *A. pavonina* has blood glucose lowering activity.

Acknowledgement
The research was carried out at the Animal house, Faculty of Medicine, University of Colombo, Sri Lanka under the supervision of Prof. Preethi Soysa and Mr. Kamal Perera.

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