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Analgesic, Antidiarrheal, Antioxidant, Cytotoxic and Oral Glucose Tolerance Activities of Ethanolic Leaf Extract of *Aristolochia indica* L.

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Abstract

Objective: To investigate the possible analgesic, antidiarrheal, antioxidant, cytotoxic and oral glucose tolerance activity of ethanolic leaf extract of *Aristolochia indica* (*A. indica*) L.

Methods: Analgesic activity was evaluated by acetic acid induced writhing method in mice. Castor oil induced diarrheal model mice were used to investigate antidiarrheal activity of the leaf extract. Qualitative *in vitro* antioxidant activity was evaluated by thin layer chromatography (TLC) technique. Cytotoxic activity was investigated on the basis of brine shrimp lethality bioassay. Finally, the hypoglycemic activity of the leaf extract was evaluated by oral glucose tolerance test.

Results: The plant extract showed dose dependent analgesic activity by acetic acid induced writhing inhibition in mice model. *In vivo* antidiarrheal activity was substantiated by significant prolongation of latent period and decreased in total number of stools compared to control. In the TLC-based qualitative antioxidant assay using 1, 1-diphenyl-2-picryl hydrazyl (DPPH), the plant extract showed the free radical scavenging properties indicated by the presence of strong yellow spot on a purple background on the TLC plate. In the cytotoxicity assay, the LC_{50} obtained for the extract was low enough which indicates that the extract may contain cytotoxic activity. The plant extract at the dose of 500 mg/kg showed significant glucose lowering activity compared to control.

Conclusion: These results suggest that the extract possesses analgesic, antidiarrheal, antioxidant, cytotoxic and oral glucose tolerance activity.

Keywords: Analgesic, Antidiarrheal, Antioxidant, Cytotoxic, Oral Glucose Tolerance, *Aristolochia indica.*

1. Introduction

Aristolochia indica L., commonly known as Ishwari, Nakuli and Gandhanakuli, is one of the 500 different species of Aristolochiaceae family. This creeper plant is distributed throughout the Mediterranean, tropical and sub-tropical countries and available in different parts of Bangladesh, India, Nepal and Sri Lanka in Indian subcontinent (Dey and De **2011**; Yasmin *et al.* **2016**). Phytoconstituents like ceryl alcohol, stigmas-4-en-3-one, β-sitosterol, friedelin etc. have been isolated from various parts of *Aristolochia indica* L. (Sati *et al.* **2011**). Isolation of sesquiterpene hydrocarbons like ishwarane and aristolochene from the roots of the plant have also been reported (Dey and De **2011**). Aristolochic acid obtained from this plant is a rodent carcinogen and thus it may have potentials for

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causing Balkan nephropathy. *Aristolochia indica* L. is also well-known for its therapeutic potentials. It is effective in the treatment of skin diseases, malaria, intermittent fever and parasitic infections. It is also used to treat intestinal disorders, oedema (Heinrich *et al.* **2009**), bacterial and fungal infections etc. (Shafi *et al.* **2002**; Kumar *et al.* **2006**). It is also used in the treatment of ailments like snake bites, indigestion, blood pressure, gastric, inflammation, bronchial asthma, scorpion stings etc. (Rastogi and Mehrotra **2001**). Again, this plant is prescribed to treat diseases like bowel troubles, ulcers, cholera, leprosy, poisonous bites etc. (Krishnaraju *et al.* **2005**; Kanjilal *et al.* **2009**). The use of this plant as emmenagogue, abortifacient, anti-inflammatory, antiseptic, antibacterial, antineoplastic and phospholipase A2 inhibitor has also been documented (Achari *et al.* **1983**; Das *et al.* **2010**).

Ancient use of this traditional medicinal plant indicates the potentials that this plant may possess some important biological properties. Previous studies have reported the antimicrobial (Kumar *et al.* **2011**), anti-spermatogenic (Pakrashi and Pakrasi **1977**), anti-diarrheal (Dharmalingam *et al.* **2014**), anthelmintic (Yasmin *et al.* **2016**), anti-inflammatory (Das *et al.* **2010**), anti-oxidant (Thirugnanasampandan *et al.* **2008**), anti-diabetic (Karan *et al.* **2012**), anti-fertility ((Pakrashi and Pakrasi **1979**), anti-oestrogenic, anti-implantation (Pakrashi and Chakrabarty **1978**) and anti-neoplasmic (Rana and Khanam **2002**) activities of different parts of this plant. However, analgesic, cytotoxic and oral glucose tolerance activities of ethanolic leaf extract of this plant have not yet been well explored. Therefore, the present study was undertaken to carry out the possible analgesic, cytotoxic and oral glucose tolerance activities along with anti-diarrheal and antioxidant activities of ethanolic leaf extract of *A. indica* L.

2. Materials and methods

2.1 Plant material collection and identification

The leaves of the plant *Aristolochia indica* L. were collected on 12th October, 2013 from Khulna district of Bangladesh at daytime. Any type of adulteration was strictly prohibited during collection of leaves. The plants were authenticated officially by the experts of Pharmacy Discipline, Khulna University, Bangladesh.

2.2 Preparation of crude extract

Undesirable materials were separated from the collected leaves. The leaves were then shed dried and coarse powder of the leaves were made with the help of a suitable grinder. 150 g of grinded leaves powder was soaked in 700 ml of ethanol in a glass container. The extract was then separated from the plant debris after 15 days by filtration with the help of Whatman filter paper. Concentrated extract was then prepared by evaporation (initially by open air and finally by water bath). The final yield in the extract was 14.67%.

2.3 Experimental animal

Young Swiss-albino mice aged 4-5 weeks with appropriate average weights of 28-35 gm were used as experimental animal for this experiment which were purchased from Department of Pharmacy, Jahangirnagar University, Bangladesh.

2.4 Phytochemical screening test

Phytochemical analysis of ethanolic leaf extract of *Aristolochia indica* L. was carried out following standard procedure (Ghani **2003**).

2.5 Evaluation of in vivo analgesic activity by acetic acid induced writhing method

Analgesic activity of *Aristolochia indica* L. leaves extract was evaluated by acetic acid induced writhing method in mice (Ahmed *et al.* **2004**; Whittle **1964**). Young Swiss-albino were randomly selected and divided into four groups denoted as group-I, group-II, group-III and group- IV consisting of 5 mice in each group. Each group received a particular treatment i.e. negative control (10 mg/kg body weight of solution prepared by mixing few drops of tween-80 with 10 ml of distilled water), positive control (25 mg/kg body weight Diclofenac Na injection) and the two doses of the extract (250 and 500 mg/kg body weight). Test samples, positive and negative control solution were given orally by means of a feeding needle. A thirty minutes interval was given to ensure proper absorption of the administered substances. Then, the writhing inducing chemical acetic acid solution (0.7%) was administered intraperitoneally to each of the animals of a group. After an interval of 5 minutes, given for absorption of acetic acid, number of squirms (writhing) was counted for 15 minutes.

2.6 Evaluation of in vivo antidiarrheal activity

Experimental animals were randomly selected and divided into six groups denoted as group-I, group-II, group-III, group- IV, group-V and group- VI consisting of 5 mice in each group. These groups received a particular treatment i.e. control, standard and the four doses of the extract respectively. Group-I considered as the control group received only distilled water containing 1% tween-80. Group-II considered as standard group received standard Loperamide at the dose of 3 mg/kg body weight as oral suspension. Group-III, Group-IV, Group-V and Group-VI were treated with suspension of extract of *Aristolochia indica* L. at the oral doses of 62.5 mg/kg body weight, 125 mg/kg body weight, 250 mg/kg body weight and 500 mg/kg body weight respectively. The mice were fed with the

samples 1 hour prior to the oral administration of castor oil at a dose of 0.7 ml per mouse. Individual mouse of each group was placed in separate cage having blotting paper in every cage lined with the floor to examine the presence of diarrhea every hour for 4 hours after the castor oil administration. Number of stools or any fluid material that stained the blotting paper were counted at each successive hour during the 4 hours period and was noted for each mouse. The latent period of each mouse was also counted. At the beginning of each hour new blotting papers were placed for the old ones.

2.7 Evaluation of in vitro antioxidant activity

The qualitative *in vitro* antioxidant activity of ethanolic extract of leaves of *Aristolochia indica* L. was evaluated by thin layer chromatography (TLC). The objective of this technique was to detect polar, non-polar and medium polar groups having antioxidant activity. Three types of solvents of different polarity were used to separate different compounds based on their polarity **(Table 1)**.

Table 1: Solvent systems

Groups	Solvent system	Ratio
Non-polar	n-Hexane : Acetone	2:1
Medium polar	$CHCl_3$: CH_3OH	5:1
Polar	$CHCl_3$:CH_3OH: H_2O	40:10:1

In this technique, a fine capillary tube was used as spotter for sample application. A very little amount of plant extract diluted with ethanol was taken and the sample was spotted in uniform size (about 0.3 cm) on TLC plates. Then, each spot was dried and chromatogram was developed by ascending technique. Here, two plates were spotted and chromatogram was run in solvent system chloroform and methanol (5:1). After developing the chromatogram, the plate was sprayed with 0.02 % 1,1-diphenyl-2-picryl hydrazyl (DPPH) solution of ethanol on it by a spray gun. Again, two plates were spotted and chromatogram was run in solvent system Chloroform: Methanol: Water (40:10:1). After developing the chromatogram, the plate was sprayed with 0.02 % DPPH solution of ethanol on it by a spray gun. The applied sample was run properly with different solvent systems and observed which solvent system separated the sample well. *Aristolochia indica* L. was well separated in the polar solvent. So, polar solvent was chosen for qualitative antioxidant test.

2.8 Evaluation of cytotoxic activity

The cytotoxic activity of ethanolic extract of leaves of *Aristolochia indica* L. was evaluated on the basis of brine shrimp lethality bioassay. First, sea water was taken in a bottle and *Artemia salina* (brine shrimp eggs) were added. The shrimps were allowed for 18 to 24 hours to hatch and mature as nauplii (larvae). The hatched shrimps were attracted to light to collect them and they were taken for bioassay. After that, 26 clean test tubes were taken, 14 of which were for the samples in different concentrations, 7 for control test corresponding the amount of dimethyl sulfoxide (DMSO) used in samples and 5 for standard in different concentrations. Each test tube was accurately marked to indicate the 5 ml volume. Then, with the help of the micropipette, 2.5 ml sample of concentration 10, 20, 40, 80, 160, 320, 640 µg/ml were added to that 7 test tubes through serial dilution method and adjusted to 5 ml with saline water to get final concentration of 5, 10, 20, 40, 80, 160, 320 µg/ml respectively. In standard test, 5 test tubes were added with 10 alive brine shrimp nauplii and adjusted to 5 ml with saline water to make final concentration of 0.312, 0.625, 1.25, 2.5, 5 µg/ml of standard (vincristine sulphate) through dilution method. The concentration of DMSO in these test tubes did not exceed 10 µl/ml. For the control, same volume of DMSO (as in the sample test tubes) were taken in the rest of the 7 test tubes and 10 alive brine shrimp nauplii were added ensuring final volume 5 ml.

After 24 hrs, the test tubes were observed and the number of survived nauplii in each test tube was counted. Then, the percentage of lethality of brine shrimp nauplii was calculated at each concentration for each sample. The test was performed in duplicate to avoid statistical error.

% Mortality = [Avg. no. of alive shrimp of control - Avg. no. of alive shrimp of sample)/ Avg. no. of alive shrimp of control] × 100

2.9 Oral glucose tolerance test

Oral glucose tolerance tests were carried out as per the procedure previously described by Joy and Kuttan (**1999**) with minor modifications. Twenty animals were randomly selected and divided into four groups consisting of five animals in each group. Each group received a particular treatment. Prior to any treatment, each mouse was properly weighed and the doses of control and test materials were adjusted properly. At zero hour, test samples at the dose of 250 mg/kg and 500 mg/kg, control (1% tween-80 solution in water) and standard drug (glibencamide) were administered orally by means of a feeding needle. After 60 minutes, all groups were treated with 10% glucose solution (2 gm/kg body weight). After glucose administration, about 30, 90 and 150 minute later, blood glucose loading were determined by collecting blood samples from tail vein. Finally, blood glucose level was measured using a glucometer.

2.10 Statistical analysis

The data were presented as mean ± SEM (n=5). Results were analyzed by one-way analysis of variance (ANOVA) followed by Turkey's multiple comparisons test. Student t test were used to compare between two

groups. The significant difference was considered at $P < 0.05$.

3. Results and discussion

3.1 Phytochemical test

Preliminary phytochemical analysis of ethanolic leaf extract of *Aristolochia indica* L. indicated the presence of reducing sugars, alkaloids, flavonoids, glycosides, tannins and steroids.

3.2 Test for analgesic activity

The acetic acid induced writhing method is an analgesic behavioral observation assessment method that demonstrates a noxious stimulation in mice. If the sample possesses analgesic activity, the animal that received the sample will give lower number of writhing than the control, i.e. the sample having analgesic activity will inhibit writhing. Both the doses of the plant extract (250 and 500 mg/kg body weight) showed significant writhing inhibition ($p<0.001$) compared to the control (**Table 2**).

3.3 Test for antidiarrheal activity

Diarrhea was considered by the presence of stool or any fluid material that stained the blotting paper placed in every cage lined with the floor. Time taken before the first defecation was considered as the 'Latent period'. The latent period and stool count after 4 hours of test group were compared with control group to evaluate antidiarrheal activity. Antidiarrheal agents increase latent period and decrease total stool count. In our experiment, we found that both the doses of ethanolic leaf extract of *Aristolochia indica* L. (250 and 500 mg/kg body weight) increased the latent period and also decreased the total stool count than the control (**Table 3 and 4**).

3.4 Test for antioxidant activity

In the TLC-based qualitative antioxidant assay using DPPH, *Aristolochia indica* L. leaves showed the free radical scavenging properties indicated by the presence of strong yellow spot on a purple background on the TLC plate (**Fig. 1**).

3.5 Test for cytotoxic activity

The LC_{50} caused by the test extract as well as vincristine sulphate as standard were calculated by probit analysis software LdP (LdP Line software, USA) and was found to be 26.2114 µg/ml for *Aristolochia indica* L. leaves extract whereas 0.4381 µg/ml for vincristine sulphate (**Table 5**). Result of this study indicates that the leaves extract of *Aristolochia indica* L. might have compounds with biological activity with actions like enzyme inhibition, ion channel interference, antimicrobial, pesticidal and cytotoxic activity. Here, both the test sample and vincristine sulphate showed a gradual increase in percent mortality of the shrimp nauplii with the increase in concentration. The LC_{50} obtained for the extract was low enough to show good cytotoxic activity.

3.6 Test for oral glucose tolerance

Aristolochia indica L. leaves extract was subjected to hypoglycemic activity test by glucose tolerance test. Test sample at the dose of 500 mg/kg showed significant glucose lowering activity compared to control. But, the rest of the dose (250 mg/kg) did not show any significant hypoglycemic activity (**Table 6**).

The present investigation highlights the hypoglycemic efficacy of leaves extract of *Aristolochia indica* L. by oral glucose tolerance test. Phytochemical analysis of the oil in this study showed the presence of bioactive components like alkaloids, tannins, steroids, flavonoids and glycosides. This findings collaborates with the earlier reports of Okokon *et al.* (**2009**) and Odoemena *et al*. (2010) on the roles of some phytochemical components inherent in plants. Alkaloids have been reported as the active ingredient in medicinal plants exhibiting potency as antibiotic, antidiabetic and insecticidal agents (Abreu and Pereiru **2001**; Odoemena *et al*. **2007**). Ahmed *et al*. (**1991**) stated that the presence of flavonoids in plant extract effectively helped in regeneration of β-cell in alloxan induced diabetic rats and also reduced the blood sugar level. This could be as a result of the insulinogenic activity of flavonoids and its beneficial effect on islet of langerhan. These constituents may in part be responsible for the observed significant activity of this extract either singly or in synergy with one another. The result of this research lend a credence that *Aristolochia indica* L. leaves extract has hypoglycemic activity.

4. Conclusion

This study suggests that the ethanolic leaf extract of *Aristolochia indica* L. possesses potent analgesic, antidiarrheal, antioxidant, cytotoxic and oral glucose tolerance activities that support this plant in traditional medicine for therapeutic purposes. However, further investigation is needed to isolate bioactive constituents responsible for versatile activities of this plant in traditional medicine.

5. Acknowledgment

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Table 2: Analgesic effects of ethanolic leaf extract of *A. indica*

Treatment group	Mean of writhing	% Inhibition of writhing
Blank control	26±2.003	00.00
Standard: Diclofenac Na (25mg/kg)	4.6±0.650***	82.31
Extract I: (250 mg/kg)	19.8±2.780***	23.85
Extract II: (500 mg/kg)	8.6±0.960***	66.92

Data are represented as Mean±SEM, n=5. ***p<0.001, significant compared to control.

Table 3: Effects of ethanolic leaf extract of *A. indica* on latent period of diarrheal induction in castor oil-induced diarrheal mice

Treatment group	Mean latent period (min)	Increase in latent period (%)
Bank control (castor oil (0.7 ml, p.o)+ vehicle, p.o)	36.2±3.54	00.00
Positive control (castor oil (0.7 ml, p.o)+ Loperamide (3 mg/kg bd wt, p.o)	191.6±3.52***	81.10
Extract I (castor oil (0.7 ml, p.o)+ Extract (250 mg/kg bd wt, p.o)	63.2±3.08***	42.72
Extract II (castor oil (0.7 ml, p.o)+ Extract (500 mg/kg bd wt, p.o)	112.6±3.64***	67.85

Data are represented as Mean±SEM, n=5. ***p<0.001, significant compared to blank control, p.o., per oral

Table 4: Effects of ethanolic leaf extract of *A. indica* on frequency of defecation in castor oil-induced diarrheal mice

Treatment group	Mean no. of stool	Inhibition of defecation (%)
Bank control (castor oil (0.7 ml, p.o)+ vehicle, p.o)	24.80±1.68	00.00
Positive control (castor oil (0.7 ml, p.o)+ Loperamide (3 mg/kg bd wt, p.o)	01.20±0.18***	95.16
Extract I (castor oil (0.7 ml, p.o)+ Extract (250 mg/kg bd wt, p.o)	07.00±0.63***	71.77
Extract II (castor oil (0.7 ml, p.o)+ Extract (500 mg/kg bd wt, p.o)	02.40±0.22***	90.32

Data are represented as Mean±SEM, n=5. ***p<0.001, significant compared to blank control, p.o., per oral

Table 5: LC_{50} for *Aristolochia indica* (test sample) and vincristine sulphate (standard) with lower and upper limit

Treatment group	LC	Conc. (µg/ml)	Lower limit (µg/ml)	Upper limit (µg/ml)
Extract	50	26.2476	8.3944	59.1295
Vincristine sulphate	50	0.4381	0.1677	0.6039

Table 6: Hypoglycemic activity of A. indica leaves extract

Group	Plasma glucose level (m mol/L)			
	Fasting state	30 min	90min	150 min
Control	3.58±0.32	11.42±0.35	7.82±0.32	6.1±0.32
Standard	3.78±0.39	2.62±0.23	2.9±0.26	3.18±0.28 *
Test 250mg/kg	3.9±0.18	7.84±0.29	6±0.39	5.28±0.37
Test 500mg/kg	2.98±0.27	6.00 ±0.26*	5.76±0.53	5.28±0.41

Values are expressed as mean ± SEM. n=5 *P<0.05 vs. control.

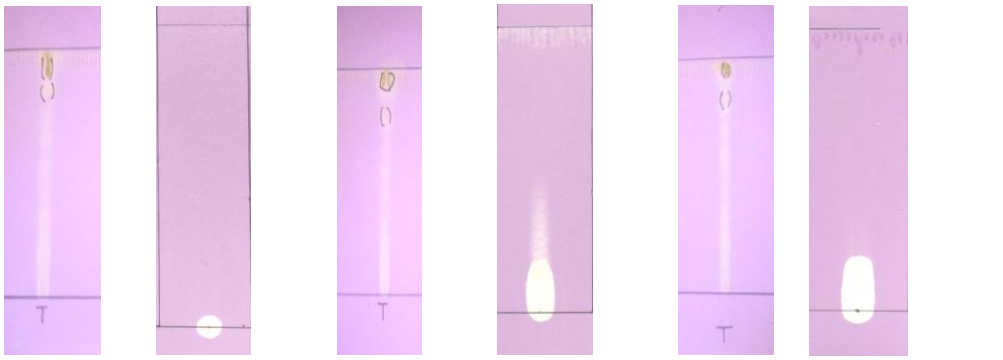

Fig 1 Comparison of TLC plate for *Aristolochia indica* L. with Standard (Ascorbic acid) after applying DPPH.

6. Abbreviations

GI: Gastrointestinal, PBS: Phosphate-buffered Saline, TLC: Thin Layer Chromatography, DPPH: 1, 1-Diphenyl-2-Picryl Hydrazyl, DMSO: Dimethyl Sulfoxide, ANOVA: One-way Analysis of Variance.

7. Conflict of interest

The authors declare no competing financial interest.

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