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EVALUATION OF PHARMACOLOGICAL ACTIVITIES OF METHANOLIC EXTRACT OF *NEPHELIUM LAPPACEUM* L. SEEDS

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ABSTRACT: The study was carried out to assess the analgesic, anti-inflammatory, CNS depressant and anti-diarrhoeal activity of methanolic extract of *Nephelium lappaceum* L. seeds (MNLS). Analgesic activity was evaluated using acetic acid-induced writhing and formalin-induced licking paw test in mice. Anti-inflammatory effect was studied using the carrageenan-induced inflammatory method. Hole cross and open field models were used to evaluate CNS depressant activity whereas castor oil-induced diarrhoeal model was employed for testing anti-diarrhoeal activity. In the analgesic activity, MNLS at a dose of 500 mg/kg exhibited potent (51.27%) activity against acetic acid-induced pain in mice whereas indomethacin (10 mg/kg) displayed 58.86% inhibition. Furthermore, the extracts showed 50.87% and 57.60% inhibition of the formalin-induced paw licking in mice at a dose of 250 and 500 mg/kg b.w. respectively and indomethacin produced 70.72% inhibition. In the carrageenan-induced paw edema test, the extract showed a significant ($p<0.05$) inhibition of paw edema after 30 min to a 4th h of the study period. In hole cross and open field tests, maximum 88.09% and 85.94% suppression of locomotor activity were observed with the higher dose (500 mg/kg) of the extract whereas suppression of the locomotor activity of the standard drug diazepam (1mg/kg) was 92.85% and 92.77% respectively, in these test. In the antidiarrhoeal activity, the extract (500 mg/kg) exhibited significant inhibition (53.46%, $p <0.001$) of fecal dropping in castor oil induced diarrhea in mice where loperamide (3 mg/kg) showed 56.43% inhibition of defecation.

INTRODUCTION: *Nephelium lappaceum* L. (*N. lappaceum*) commonly known as rambutan, is a medium-sized tropical tree belonging to the Sapindaceae family. The fruit produced by the tree is also known as rambutan [1].

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Traditionally the root extract was used to treat fever, and bark extract for tongue diseases. A poultice of crushed leaves was used to relieve a headache by placing it on the head. The seeds are edible when roasted, they are bitter and said to be narcotic.

The peel and seed extract of *N. lappaceum* are reported to possess antioxidant, and antibacterial activities [2, 3, 4]. Anticancer activity was reported for the fruit peel extract of *N. lappaceum* [5]. Rajasekaran *et al*., (2013) was reported the plant contains an alkaloid, glycoside, saponin, steroids,

and tannin [6]. Reported [7] anti-hypercholesterolemic activities for *N. lappaceum* and reported [8] the presence of more than 100 volatiles in the ethyl acetate fruit extract of *N. lappaceum*, detected by GC/MS.

The 20 most potent odorants included a-damascenone, (E) - 4, 5 - epoxy - (E) - 2 - decenal, vanillin, (E) - 2 - nonenal, phenyl acetic acid, cinnamic acid, ethyl 2-methyl butyrate, and a-decalactone. Dichloromethane extracts of the seeds of *N. lappaceum* reported to possess two new diastereomeric monoterpene lactones, and the known butenolide siphonodin, as well as kaempferol 3 - O - beta - D - glucopyranoside - 7 - O - alpha - L - rhamnopyranoside [9]. As a part of our continuing studies [10, 11] on natural products for their pharmacological properties we investigated methanolic seeds extracts of *N. lappaceum* for its analgesic, anti-inflammatory, CNS depressant and anti-diarrhoeal activities.

MATERIALS AND METHODS:

Chemicals and Drugs: Indomethacin, diazepam, loperamide and castor oil were purchased from local market manufactured by Square Pharmaceuticals Ltd., Bangladesh.

Collection of the Plant: The plant was collected from the district of Dhaka, Bangladesh. The plant was identified in Bangladesh National Herbarium Mirpur, Dhaka, and accession number was 36, 663. The plant part (seeds) was thoroughly washed with water, cut into small pieces and dried in the sun.

Extraction of the Plant Material: After drying, the seeds were reduced to coarsely powder using a grinding mill. 140 gm powder was extracted with a mixture of methanol: water (9.5:5, v/v) by a cold extraction method. The solvent was completely removed and obtained 25 gm (yield = 17.85%) dried crude extract which was used for investigation.

Animal: For the experiment Swiss albino mice of either sex, 3-4 weeks of age, weighing between 20-25 gm, were collected from the animal research branch of the International Center for Diarrheal Disease and Research, Bangladesh (ICDDR, B). Animals were maintained under standard environmental conditions (temperature: (24.0 ± 1.0°C), relative humidity: 55-65% and 12h light/ 12h dark cycle) and had free access to feed and water *ad libitum*. The animals were acclimatized to laboratory condition for one week before experimentation [12].

All protocols for the animal experiment were approved by the Institutional Animal Research Ethics Committee.

Experimental Groups: The animals were divided into control, standard and test groups containing six mice of each.

Acute Toxicity Study: Mice were divided into control and test groups (n=6). The test groups received the extract per orally at the doses of 500, 1000, 1500 and 2000 mg/kg. Then the animals were kept in separate cages and were allowed to food and *ad libitum*. The control group received the water. The animals were observed for possible behavioral changes, allergic reactions, and mortality for the next 72 h [13].

Analgesic Activity:

Acetic Acid-Induced Writhing Test: The analgesic activity of the samples was also studied using the acetic acid-induced writhing model in mice. Test samples and vehicle were administered orally 30 min before intraperitoneal administration of 0.7% acetic acid, but Diclofenac-Na was administered intraperitoneally 15 min before injection of acetic acid. After 5 min, the mice were observed for specific contraction of the body referred to as 'writhing' for the next 10 min [14].

Formalin-Induced Paw Licking Test: The anti-nociceptive activity of the drugs was determined using the formalin test described by [15]. The control group received 5% formalin. Twenty µl of 5% formalin was injected into the dorsal surface of the right hind paw 60 min after administration of methanolic extracts of *Nephelium lappaceum* (250 and 500 mg/kg, p.o.) and indomethacin (10 mg/kg, i.p.). The mice were observed for 30 min after the injection of formalin and the amount of time spent licking the injected hind paw was recorded.

The first 5 min post formalin injection was referred to as the early phase and the period between 15 and 30 min as a late phase. The total time spent licking or biting the injured paw (pain behavior) was measured with a stopwatch.

Anti-Inflammatory Activity:

Carrageenan-Induced Paw Edema in Mice: Carrageenan-induced paw edema was done through the method of [16] the inflammation was induced through injecting 0.1 ml of freshly prepared carrageenan (1%) aqueous suspension in normal saline underneath the plantar tissue of the right hind paw of the mice. The different groups of mice were administered with MNLS (250 and 500 mg/Kg, p.o.) and indomethacin (10 mg/kg, i.p.).

The control group received vehicle (10 ml/kg, p.o.). 1 h after the drug treatment and the paw edema was induced through the injection of carrageenan (an edematogenic agent). The paw volume was measured using a plethysmometer. The measures were determined at 0 min (Vo: before the edematogenic agent injection) and 30 min 1, 2 and 4 h later (Vt). The difference between Vt and Vo was taken as the edema value. The percentage of inhibition was calculated according to the following formula:

% Inhibition = (Vt-Vo) control - (Vt-Vo) treated (Vt-Vo) control ×100

CNS Depressant Activity:

Hole Cross Test: The method was adopted as described by [17]. A steel partition was fixed in the middle of a cage having a size of 30 × 20 × 14 cm. A hole of 3 cm diameter was made at the height of 7.5 cm in the center of the cage. The number of passage of a mouse through the hole from one chamber to other was counted for 3 min at 0, 30, 60, 90 and 120 min after oral administration of the test drugs.

Open Field Test: This experiment was carried out as described by [18]. The animals were divided into control and test groups containing five mice each. The test group received *N. lappaceum* extract at the doses of 250 and 500 mg/kg body weight orally whereas the control group received vehicle (1% tween 80 in water).

The floor of an open field of half square meter was divided into a series of squares each alternatively colored black and white. The apparatus had a wall of 40 cm height. The number of squares visited by the animals was counted for 3 min at 0, 30, 60, 90, and 120 min after oral administration of the test drugs.

Anti-Diarrhoeal Activity:

Effect of Extract on Castor Oil-Induced Diarrhoea: The method described by Dash *et al.* (2014) [11, 19] was adopted to study the effect of the *N. lappaceum* extract on castor oil-induced diarrhea. Mice were weighed and grouped into 4 groups (n = 6). Group 1 received distilled water, group 2 and 3 were administered 250, and 500 mg/kg extract orally while group 4 received loperamide (3 mg/kg) orally. Each animal was then given 0.3 ml of castor oil orally after 1 h of treatment and placed in transparent cages to observe for consistency of fecal matter and frequency of defecation for 4 h. The percent (%) inhibition of defecation was measured using the following formula:

$$\% \text{ Inhibition of defecation} = [(A - B) / A] \times 100$$

Where, A = Mean number of defecation caused by castor oil, B = Mean number of defecation caused by drug or extract.

RESULTS:

Acute Toxicity: Oral administration of MNLS at the doses of 500-2000 mg/kg did not produce any mortality or noticeable behavioral changes in mice within 72 h observation period. Therefore, it can be suggested that MNLS have low toxicity profile with LD_{50} greater than 2000 mg/kg.

Acetic Acid-Induced Writhing Test: The result of the effect of MNLS against acetic acid-induced writhing in mice is shown in **Table 1**. The MNLS (250 and 500 mg/kg) dose-dependently reduced acetic acid-induced abdominal constrictions and stretching. The reduction was statistically significant ($p<0.001$) when compared with control.

Formalin-Induced Paw Licking Test: The result of the effect of the MNLS against formalin-induced hind paw licking in mice is shown in **Table 2**. The MNLS (250 and 500 mg/kg) pre-treated animals showed a significant ($p<0.05$) dose-related reduction of the hind paw licking caused by formalin when compared with control and MNLS treated with the dose of 500 mg/kg showed maximum. In this study, indomethacin (10 mg/kg) was used as standard

Carrageenan-Induced Paw Edema in Mice: The result of the effect of MNLS on carrageenan-

induced edema is shown in **Table 3**. The MNLS exerted a significant ($p<0.05$) anti-inflammatory effect at the dose of 250 and 500 mg/kg and was comparable to that of the control group. The maximum percentage inhibition activity of MNLS (250 and 500 mg/kg) and standard (Indomethacin) 10 mg/kg were found to be 23.11%, 28.99%, and 41.59%, respectively.

TABLE 1: EFFECTS OF THE METHANOLIC EXTRACT OF *N. LAPPACEUM* ON ACETIC ACID-INDUCED WRITHING IN MICE

Groups	Dose (mg/kg)	No. of writhing	% of writhing	% of writhing inhibition
Control	10 ml/kg	26.33±0.56	100	-
Standard	10	10.83±0.31**	41.13	58.86
MNLS	250	17.33±0.56**	65.82	34.18
	500	12.83±0.48**	48.72	51.27

Indomethacin was administered 15 min before 0.7% acetic acid administration. Writhing was counted for 15 min, starting after 5 min of acetic acid administration. Values are mean ± SEM, (n = 6); ** p< 0.001, Dunnett test as compared to control. Control received vehicle (1% Tween 80 in water), Standard received Indomethacin 10 mg/kg body weight, MNLS was treated with 250 and 500 mg/kg body weight (p.o.) of the extract of *Nephelium lappaceum.* MNLS = Methanolic extract of *Nephelium lappaceum* L. seeds.

TABLE 2: EFFECTS OF THE METHANOLIC EXTRACT OF *N. LAPPACEUM* ON HINDPAW LICKING IN THE FORMALIN TEST IN MICE

Groups	Dose (mg/kg)	Early Phase 0-5 min	Late Phase 15-30 min
Control	10 ml/kg	25±1.03	46±1.03
Standard	10	12.16±0.40*(51.36%)	21.83±0.70*(52.50)
MNLS	250	19.17±0.31*(23.32)	22.6±0.56*(50.87)
	500	15.67±0.42*(37.32)	19.5±0.56*(57.60)

Control received vehicle (1% Tween 80 in water), Standard received Indomethacin 10 mg/kg body weight, MNLS was treated with 250 and 500 mg/kg body weight (p.o.) of the extract of *Nephelium lappaceum.* Values are mean ± SEM, (n = 6); * p< 0.05, Dunnet't test as compared to control. MNLS = Methanolic extract of *Nephelium lappaceum* L. seeds.

TABLE 3: ANTI-INFLAMMATORY EFFECTS OF THE METHANOLIC EXTRACT OF *N. LAPPACEUM* ON CARRAGEENAN PAW EDEMA IN MICE

Groups	Dose (mg/kg)	After treatment in inflamed in mice (% of inhibition)				
		0 min	30 min	1 h	2 h	4 h
Control	10 ml/kg	2.36±0.01	2.67±0.01	2.41±0.01	2.39±0.01	2.38±0.01
Standard	10	1.99±0.01	1.78±0.02* (33.33%)	1.65±0.02* (31.53%)	1.45±0.02* (39.33%)	1.39±0.02* (41.59%)
MNLS	250	2.35±0.02	2.44±0.01* (8.61%)	2.23±0.01* (7.46%)	1.97±0.01* (17.57%)	1.83±0.02* (23.11%)
	500	2.18±0.01	2.01±0.03* (24.72%)	1.87±0.03* (21.86%)	1.76±0.03* (26.36%)	1.69±0.02* (28.99%)

Control received vehicle (1% Tween 80 in water), Standard received Indomethacin 10 mg/kg body weight, MNLS was treated with 250 and 500 mg/kg body weight (p.o.) of the extract of *Nephelium lappaceum.* Values are mean ± SEM, (n = 6); * p< 0.05, Dunnet't test as compared to control. MNLS = Methanolic extract of *Nephelium lappaceum* L. seeds.

Hole Cross Test: Results of the hole-cross test of MNLS are given in **Table 4**. They were statistically significant ($p<0.001$) for all dose levels at 30, 60, 90 and 120 min and followed a dose-dependent response. The depressing effect was most intense at dose 500 mg/kg.

TABLE 4: CNS DEPRESSANT EFFECTS OF THE METHANOLIC EXTRACT OF *N. LAPPACEUM* ON HOLE CROSS TEST IN MICE

Groups	Dose (mg/kg)	Number of movements (% of inhibition)				
		0 min	30 min	60 min	90 min	120 min
Control	10 ml/kg	16.8±0.66	16.2±0.73	14.2±0.96	15.8±0.58	16.8±1.15
Standard	10	15.6±0.86	6.8±0.58** (58.02%)	4.2±0.34** (70.42%)	2.8±0.58** (82.27%)	1.2±0.37** (92.85%)
MNLS	250	15.8±0.58	12.4±0.81** (23.45%)	8.8±0.80** (38.02%)	7.4±0.40** (53.14%)	4.6±0.24** (72.62%)
	500	17.2±0.86	11.4±0.74** 29.63%)	5.8±0.58** (59.15%)	3.2±0.48** (79.74%)	2±0.31** (88.09%)

Control received vehicle (1% Tween 80 in water), Standard received diazepam 1 mg/kg body weight, MNLS was treated with 250 and 500 mg/kg body weight (p.o.) of the extract of *Nephelium lappaceum.* Values are mean ± SEM, (n = 6); ** p< 0.001, Dunnet't test as compared to control. MNLS = Methanolic extract of *Nephelium lappaceum* L seeds.

Open Field Test: Results of the open-field test of MNLS are given **Table 5**. The MNLS extract exhibited a decrease in the movements of the test animals at all dose levels. The results were statistically significant ($p<0.05$-0.001) for all doses at 120 min and followed a dose-dependent response.

TABLE 5: CNS DEPRESSANT EFFECTS OF THE METHANOLIC EXTRACT OF *N. LAPPACEUM* ON OPEN FIELD TEST IN MICE

Groups	Dose (mg/kg)	Number of movements (% of inhibition)				
		0 min	30 min	60 min	90 min	120 min
Control	10 ml/kg	151±2.2	149.8±1.74	149.4±2.91	147.8±1.56	152.2±2.87
Standard	10	161.5±4.06	86.2±1.74** (42.45%)	63.8±1.50** (57.29%)	43.0±1.10** (70.90%)	11.0±0.89** (92.77%)
MNLS	250	167.6±1.63	105.0±2.24** (29.90%)	81.8±0.92** (45.24%)	53.6±1.44** (63.73%)	34.6±1.33** (77.26%)
	500	161.0±2.07	87.0±0.89** (41.92%)	65.8±0.66** (55.95%)	46.0±0.71** (68.87%)	21.4±1.03** (85.94%)

Control received vehicle (1% Tween 80 in water), Standard received Diazepam 1 mg/kg body weight, MNLS was treated with 250 and 500 mg/kg body weight (p.o.) of the extract of *Nephelium lappaceum.* Values are mean ± SEM, (n = 6); **p< 0.001, Dunnet't test as compared to control. MNLS = Methanolic extract of *Nephelium lappaceum* L. seeds.

Castor Oil-Induced Diarrhea: In the castor oil-induced diarrhea experiment, the mice group that did not receive the plant extract showed typical diarrhoeal signs and symptoms such as watery and frequent defecation. In this test, the extracts showed significant ($p<0.001$) and dose-dependent reduction in fecal dropping **Table 6**. At 500 mg/kg dose, showed maximum 53.46 % inhibition of defecation.

TABLE 6: EFFECTS OF THE METHANOLIC EXTRACT OF *N. LAPPACEUM* ON CASTOR OIL-INDUCED DIARRHOEA IN MICE

Group	Dose (mg/kg)	No. of faeces in 4 h	% Inhibition of defecation
Control	10 ml/kg	20.2±1.28	---
Standard	3	8.8±0.86**	56.43
MNLS	250	11.8±0.37**	41.58
	500	9.4±0.24**	53.46

Control received vehicle (1% Tween 80 in water), the standard group received Loperamide 3 mg/kg body weight (p.o.), MNLS was treated with 250 and 500 mg/kg body weight (p.o.) of the extract of *Nephelium lappaceum.* Values are mean ± SEM, (n = 6); ** p< 0.001, Dunnet't test as compared to control. MNLS = Methanolic extract of *Nephelium lappaceum* L. seeds.

DISCUSSION: The present study demonstrates that MNLS possesses potent analgesic, anti-inflammatory, CNS depressant and anti-diarrhoeal activities in the tested animal models. No acute toxicity was observed after oral administration of MNLS even at the dose of 2000 mg/kg in mice. Acetic acid-induced pain by enhancing levels of PGE2 and PGF2α [20] at the receptors of the peritoneal cavity [21, 22].

The acetic acid acts indirectly by increasing the release of endogenous mediators leading to stimulation of the nociceptive neurons which are sensitive to most of the non-steroidal anti-inflammatory drugs. Two different doses (250 and 500 mg/kg b.w.) of crude extract of MNLS showed significant (34.18% and 51.27% inhibition) analgesic activity while higher doses (500 mg/kg, 51.27% inhibition) were found to exhibit potent analgesic activity against acetic acid-induced pain in mice where the reference drug indomethacin (10 mg/kg) was 58.86% inhibition **Table 1**. This result suggests the involvement of peripheral mechanisms of analgesia.

The formalin test is another important model of analgesic which is better related to clinical pain [23, 24]. This method elucidates central and peripheral activities. Formalin-induced nociception is biphasic in which the first phase involves direct stimulation of sensory nerve fibers representing neuropathic pain and the second phase involves inflammatory pain mediated by prostaglandin, serotonin, histamine, bradykinin, and cytokines such as IL-1β, IL-6, TNF-α, eicosanoids, and NO [25-30]. Therefore, the results 52.50 % and 57.60% inhibition **Table 2** shown by MNLS (250 and 500 mg/kg) suggest that the extract contains bioactive compound(s) with

peripheral anti-nociceptive actions. The ability of MNLS to inhibit chemically induced nociceptive processes tested in this study presents its potential to be used as an analgesic agent.

Carrageenan-induced paw edema has been commonly used as an experimental animal model for acute inflammation and is believed to be biphasic in which the early phase (0-5 min) of the carrageenan model is mainly mediated by histamine, serotonin, and increased synthesis of prostaglandins in the damaged tissue surroundings and the late phase is sustained by prostaglandin release and mediated by bradykinin, leukotrienes, polymorphonuclear cells, and prostaglandins produced by tissue macrophage [31, 32].

In our study, the crude extract (250 and 500 mg/kg) of MNLS exhibited significant inhibition ($p<0.005$) of paw edema at the 4th hour while the standard indomethacin reported 41.59 % inhibition **Table 3**. The possible mechanism of the observed anti-inflammatory activity might be its ability to reduce the release of histamine, serotonin or kinin-like substances or biosynthesis of prostaglandins which is consistent with the test of analgesic activity.

Rearing of mice is considered as a function of the excitability level of the CNS [33]. The decrease in rearing and locomotion in hole cross and open field tests, therefore, confirms the CNS depressant activity of MNLS. In hole cross and open field tests, maximum 88.09% and 85.94% suppression of locomotor activity were observed with the higher dose (500 mg/kg) of the extract whereas suppression of locomotor activity of the standard drug Diazepam (1 mg/kg) was 92.85% and 92.77% respectively, in these test **Table 4** and **Table 5**.

The depressant activity may be due to the presence of alkaloids in the extracts [34]. This general depressant and sedative effect of the extracts may be due to the action of alkaloids on the cerebral mechanism involved in the regulation of sleep [35]. Tannins have also been reported to show nonspecific CNS depression in mice [36]. So, the reported central depressant effect of the extracts of MNLS may be due to the presence of tannin-like constituents in the plant.

The inhibition of diarrhea in mice, induced by castor oil is used to determine the anti-diarrhoeal activity of plant extracts. Castor oil stimulates the release of prostaglandin E in the colon [36] decreases Na^+, K^+ ATPase activity [38] and alters the intestinal histology and permeability [38]. These reduce or reverse absorption of water and electrolytes from the intestinal lumen and colon and cause secretory diarrhea in mice. In this study, the extracts (250 and 500 mg/kg) showed a dose-dependent reduction in fecal droppings in castor oil-induced diarrhea. Maximum 53.46% inhibition of defecation was observed with 500 mg/kg body weight of the extract where loperamide (3 mg/kg) showed 56.43% inhibition of defecation **Table 6**.

Preliminary phytochemical screening reported the presence of alkaloid, glycoside, saponin, steroids, and tannin in the extracts [6]. These phyto-constituents may be attributed to the anti-diarrhoeal effects in the animal model. Tannins may impart anti-diarrhoeal effect possibly by inhibiting the intestinal motility [40] and reducing the intestinal secretion [41]. It may be possible that the anti-diarrhoeal activity and other pharmacological activities are due to the presence of tannins [42,] alkaloids [43], glycosides [44] and other phyto-constituents in the extracts of the plant.

CONCLUSION: The present study enabled us to conclude that the methanolic extracts of *Nephelium lappaceum* L. seeds have shown *in-vivo* potent analgesic, anti-inflammatory, CNS depressant and anti-diarrhoeal effects. Extensive research is needed to determine the individual component responsible for such activity and molecular mechanism responsible for the same.

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CONFLICT OF INTEREST: Nil

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