



Research Paper

Antinociceptive effect of ethanol extract of leaves of *Lannea coromandelica*

Mohammad Zafar Imam*, Md. Moniruzzaman

Department of Pharmacy, Stamford University Bangladesh, 51, Siddeswari Road, Dhaka 1217, Bangladesh

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ABSTRACT

Ethnopharmacological relevance: *Lannea coromandelica* (Houtt.) Merr. is a plant locally called “Jiga”, found all over Bangladesh. Leaf of the plant is traditionally used in the treatment of local swellings, pains of body, toothache etc. This study evaluated the antinociceptive effect of the ethanol extract of *L. coromandelica* leaves (EELC).

Materials and methods: The antinociceptive activity of the extract (at the doses of 50, 100, and 200 mg/kg) was evaluated by using chemical- and heat-induced pain models such as acetic acid-induced writhing, hot plate, tail immersion, formalin, and glutamate test. To verify the possible involvement of opioid receptor in the central antinociceptive effect of EELC, naloxone was used to antagonize the effect. Besides, the involvements of ATP-sensitive K^+ channel and cGMP pathway were also justified by using glibenclamide and methylene blue.

Results: EELC demonstrated significant dose-dependent antinociceptive activity in the chemical- and heat-induced nociception in mice models ($p < 0.05$). These findings imply the involvement of both peripheral and central antinociceptive mechanisms. The use of naloxone confirmed the association of opioid receptors in the central antinociceptive effect. EELC also showed the involvements of ATP-sensitive K^+ channel and cGMP pathway for antinociceptive activity.

Conclusions: This study reported the antinociceptive activity of the leaf of *L. coromandelica* and rationalized the traditional use of the leaf in the treatment of different painful conditions.

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1. Introduction

Lannea coromandelica (Houtt.) Merr. (Family-Anacardiaceae) is a small deciduous tree, locally known as Jiga in Bangladesh, which is cultivated mainly for living fence posts. Different parts of the plant are used in different ailment in the traditional medicine of the country. Leaf of the plant is traditionally used in injury, hematochezia (Zheng and Xing, 2009). Twigs are used as tooth-stick, bark for skin diseases, brew, tender leaves and root for stomachache (Franco and Narasimhan, 2009). Boiled leaves are applied to local swellings and body pain (Chopra et al., 1956; Yusuf et al., 2009). The bark is used to treat dyspepsia, general debility, gout, dysentery (Kadir et al., 2013), bruises, wounds, sores, ulcers, sore eyes, gout, swelling and body pain (Singh and Singh, 1994), eruption of skin, ulcers, and toothache (Khan et al., 2009). The sap of the fruit with common salt is used to treat cold and cough (Reddy et al., 2006). Based on the traditional uses researchers have studied the validity of its uses in different diseases. The bark has

shown anti-inflammatory (Singh and Singh, 1994), hypotensive (Singh and Singh, 1996), antihyperglycemic (Mannan et al., 2010), wound healing, antimicrobial (Sathish et al., 2010), antioxidant and analgesic activity (Alam et al., 2012). Polyflavonoid tannin in the bark with zoosporicidal activity has been reported (Islam et al., 2002). The leaf extract possess antidiarrhoeal (Panda et al., 2012) and anti-inflammatory activity (Gandhidasan et al., 1991). A number of phytochemicals have been isolated from the plant. Leaf and flower contain quercetin-3-arabinoside and ellagic acid (Subramanian and Nair, 1971). Phlobatannin and leucocyanidin have also been isolated from the flower (Nair et al., 1963). Isolated compound from bark includes β -sitosterol, physcion and physcion anthranol B, (Subramanian and Nair, 1971) and dihydroflavonols such as (2R,3S)-(+)-3',5'-dihydroxy-4',7'-dimethoxydihydroflavonol and (2R,3R)-(+)-4',5,7-trimethoxydihydroflavonol and (2R,3R)-(+)-4',7-di-O-methylidihydroquercetin, (2R,3R)-(+)-4',7-di-O-methylidihydrokaempferol and (2R,3R)-(+)-4'-O-methylidihydroquercetin (Islam and Tahara, 2000).

The use of *L. coromandelica* leaves in different painful conditions in folk medicine and lack of scientific study reporting its antinociceptive activity convinced us to design the present study to evaluate the effect of ethanol extract of *L. coromandelica* leaves

* Corresponding author. Tel.: +88 01816684184; fax: +88 02 9355967176.

E-mail address: zafarimam@gmail.com (M.Z. Imam).

using different pain models in mice. The present study also further investigated the possible mechanism(s) of action that participate in the EELC-induced antinociception.

2. Materials and methods

2.1. Plant material and extraction

The leaves of *L. coromandelica* were collected from the Shitalakkha barrage side of Demra, Dhaka in May 2012. The samples were then identified by Bushra Khan, Principal Scientific Officer, Bangladesh National Herbarium, Mirpur, Dhaka, Bangladesh. A voucher specimen (DACB: 37549) has been deposited in the Herbarium for further reference. Powdered dried leaves (250 g) were macerated with 420 ml of ethanol with occasional stirring at $25 \pm 2^\circ\text{C}$ for 3 days. The extract was then filtered using a Buchner funnel and cotton filter. The solvent was completely removed by rotary evaporator and 9.44 g extract (Yield 3.78%) was obtained. This crude extract was used for the acute toxicity and antinociceptive activity studies.

2.2. Chemicals and drugs

The following drugs and chemicals were used in the current study: morphine sulfate, diclofenac sodium (Square Pharmaceuticals Ltd., Bangladesh), naloxone (Hamein Pharmaceuticals GmbH), acetic acid (Merck, Germany), ethanol (Merck, Germany), formalin (Merck, Germany), methylene blue (Merck, Germany), L-glutamic acid (Merck, Germany), glibenclamide (Square Pharmaceuticals Ltd., Bangladesh), dimethylsulfoxide (DMSO) (Merck, Germany).

2.3. Animals

Swiss albino mice (20–25 g) of both sex were collected from the Animal Resources Branch of the International Center for Diarrheal Disease Research, Bangladesh (ICDDR,B). The animals were kept in standard laboratory conditions (relative humidity 55–60%; room temperature $25 \pm 2^\circ\text{C}$; 12 h light/dark cycle) and were provided with standard diet (ICDDR,B formulated) and clean water *ad libitum*. The animals were acclimatized to the laboratory environment for a period of 14 days before performing experiments. All the experimental animals were treated following the Ethical Principles and Guidelines for Scientific Experiments on Animals (1995) formulated by The Swiss Academy of Medical Sciences and the Swiss Academy of Sciences. The experimental processes were approved by the Institutional Ethics Committee (SUB/IAEC/12.01). AVMA Guidelines for the Euthanasia of Animals: 2013 Edition was followed in euthanasia of mice using Pentobarbital.

2.4. Drugs and treatments

EELC was dissolved in dimethylsulfoxide (DMSO) and orally administered to the test animals 30 min before the experiments at the doses of 50, 100, and 200 mg/kg body weight in both the chemical-induced pain and heat-induced pain models. The standard drug morphine sulfate (5 mg/kg) used in hot plate and tail immersion tests and diclofenac sodium (10 mg/kg) in writhing and licking tests were prepared with saline water and administered intraperitoneally 15 min before the experiments while the animals in control group received vehicle (DMSO) orally at the dose of 10 ml/kg body weight 30 min before the experiments. Naloxone, a non-selective opioid receptor antagonist, was injected intraperitoneally at 2 mg/kg dose 15 min before the administration of morphine sulfate or EELC (50, 100, and 200 mg/kg) to investigate

the involvement of opioid receptor system. Methylene blue, a non specific inhibitor of NO/guanylyl cyclase (20 mg/kg) and glibenclamide, an ATP-sensitive K^+ channel inhibitor (10 mg/kg) were also injected intraperitoneally to verify the involvement of cGMP and ATP-sensitive K^+ channel pathway respectively.

2.5. Acute toxicity test

Swiss albino mice were divided into control and three test groups which contain five animals each. EELC was administered orally at the doses of 1000, 2000, and 3000 mg/kg. The mice were allowed food and water *ad libitum* and all animals were observed for abnormal behaviors, allergic symptoms and mortality for the next 72 h (Walker et al., 2008).

2.6. Phytochemical screening

The crude ethanol extract of *L. coromandelica* (EELC) leaves were qualitatively tested for the detection of carbohydrates, saponins, flavonoids, tannins, alkaloids, glycosides, glucosides, reducing sugars, proteins, gums, and steroids following standard procedures (Ghani, 2003).

2.7. Antinociceptive activity test

2.7.1. Hot plate test

The mice that showed forepaw licking, withdrawal of the paw (s) or jumping response within 15 s on hot plate kept at a temperature of $50 \pm 0.5^\circ\text{C}$ were selected for this study 24 h prior to the experiment. Mice were fasted overnight with water given *ad libitum*. The animals were treated with morphine or EELC and were placed on Eddy's hot plate (Kshitij Innovations, Haryana, India) kept at a temperature of $50 \pm 0.5^\circ\text{C}$. A cut off period of 20 s was maintained to avoid paw tissue damage (Eddy and Leimbach, 1953). The response in the form of forepaw licking, withdrawal of the paw(s) or jumping was recorded at 30, 60, 90, and 120 min following treatment. Then the percentage of the maximal possible effect (% MPE) was calculated using the following formula: % MPE = $[(\text{Postdrug latency}) - (\text{Predrug latency}) / (\text{Cut off time}) - (\text{Predrug latency})] \times 100$.

2.7.2. Tail immersion test

To evaluate the central analgesic property the tail immersion test was performed. This procedure is based on the observation that morphine like drugs prolongs the tail withdrawal time from hot water in mice (D'Amour and Smith, 1941). One to two cm of tail of the mice pretreated with morphine or EELC were immersed in warm water kept constant at $54 \pm 0.5^\circ\text{C}$. The latency between tail sub-mersion and deflection of tail was recorded. Mice that showed a latency period between 1.5 and 3.5 s were selected for this experiment and the pre-treatment latency was recorded. A latency period of 20 s was maintained to avoid tail tissue damage in mice. The latency period of the tail-withdrawal response was taken as the index of antinociception and was determined at 30, 60, 90, and 120 min after the administration of the drug and extract. Then the % MPE was calculated from using the same formula used in hot plate test.

2.7.3. Acetic acid-induced writhing test

The mice were treated with drug or EELC and then the writhing was induced by injecting 0.6% acetic acid after 15 and 30 min, respectively, at the dose 10 ml/kg body weight. Five minutes after the injection of acetic acid, the mice were observed and the number of writhing was counted for 30 min (Sulaiman et al., 2010). The contractions of the abdomen, elongation of the body,

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