

Evaluation of Analgesic and Anti-diarrheal Activity of Ethanolic Extract of *Swietenia mahagoni* (Meliaceae) Leaves

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Abstract—

Objective: The present study was aimed to investigate analgesic and anti-diarrheal activities of ethanolic extracts of *Swietenia mahagoni* leaves using experimental models.

Methods: Analgesic activity of *S. mahagoni* leaves was tested by acetic acid-induced writhing test at a dose of 100 and 200 mg/kg and formalin-induced hind paw-licking at 150 and 300 mg/kg administered orally where Indomethacin (10 mg/kg) was used as a standard analgesic drug. Anti-diarrheal activity was investigated using castor oil-induced diarrhea through oral administration of extracts at a dosage of 250 and 500 mg/kg. Loperamide (5 mg/kg) was used as a standard drug in this method.

Results: In acetic acid-induced writhing test, ethanolic extract of *S. mahagoni* leaves showed maximum percentages of pain inhibition (56.14%) at 200 mg/kg dose in a dose-dependent manner where standard (Indomethacin) was 77.19%. The formalin-induced hind paw-licking test of *S. mahagoni* leaves showed 43.08% inhibition in early phase where standard (Indomethacin) was 76.92% and in the late phase, 34.88% inhibition at 300 mg/kg dose where standard (Indomethacin) was 58.14%. In castor oil-induced anti-diarrheal test, ethanolic extract of *S. mahagoni* leaves showed 88.89% inhibition at 250 mg/kg and 94.45% inhibition at 500 mg/kg dose which was exactly the same of standard (Loperamide) inhibition.

Conclusions: The current study indicates that ethanolic extract of *S. mahagoni* leaves have moderate analgesic and potential anti-diarrheal activity that support to the ethnopharmacological uses of this plant.

Keywords— Analgesic; Anti-diarrheal; Pain Inhibition; *Swietenia mahagoni*.

I. INTRODUCTION

For the management of pain and inflammation, either narcotic drugs e.g. opioids or non-narcotic drugs e.g. salicylates and corticosteroids are used at present [1] which are not fully satisfactory in all cases due to their adverse side effects, for example gastric lesions, ulcers, hypertension and cardiac abnormalities are caused by non-steroidal anti-inflammatory drugs and opiates [2,3]. Hence, development of newer analgesic drugs with lesser side effects is crucial. Large source of structurally novel compounds are available in medicinal plants that might help in the advancement of new drugs. According to World Health Organization (WHO), around 80% of the world's population fulfills their primary health care needs by using traditional medicine. Since prehistoric period herbal medicine has been widely used due to their availability and safety [4]. Diarrheal disease is another common disease, responsible for the death of millions of people each year which is mostly prevalent in developing countries especially in children [5]. Most people in the developing countries depend on herbal drugs for the management of diarrhoea. For this reason, World Health Organization has encouraged using traditional medicines in the treatment and prevention of this disease [6].

Swietenia mahagoni (*S. mahagoni*) is a moderate to massive evergreen plant commonly known as "mahagni" in bengali which is one of the species of genus *Swietenia* and belongs to

chinaberry family, Meliaceae. It is an endemic plant of West Indies and also known as West Indies mahogany, caoba, caoba, dominicana or acajou [7]. Different parts of this plant used traditionally for variety of diseases. The leaves have been used for Diarrhea, febrifuge, colds and catarrh. As an astringent for wound, Bark is used. The seed's use found in leishmaniasis, abortion medicine, cancer, amoebiasis, coughs, chest pains, intestinal parasitism, hypertension, diabetes and malaria in Indonesia and also in skin cuts, itches and wounds to improve the healing process in African countries [8]. The uses of this plant as traditional medicine substantiate that it may contain some significant biological activities. Although Antibacterial activity [9,10], Antimicrobial Activity [11,9], Antioxidant activity [12], Cytotoxic activity [10], Anti-ulcer activity [13], Antifungal activity [14], Anti-HIV activity [15] of *S. mahagoni* were investigated earlier but analgesic and anti-diarrheal activity has not yet been reported. Therefore the present study was carried out to investigate possible analgesic and anti-diarrheal activity of ethanolic extract of *S. mahagoni* leaves in experimental animal.

II. MATERIALS AND METHODS

Plant Material Collection and Extraction:

The leaves of *S. mahagoni* were collected from Banani Rail crossing, Dhaka, Bangladesh in October 2017. Then leaves were taken to Bangladesh National Herbarium to

confirm the specimen to be claimed *S. mahagony* and it was confirmed by the index code which was 41629. The leaves of *S. mahagony* were shed dried (600 gm) which were grinded in the blender to make powder and mixed with ethanol (solvent) to make 1.8 L solution. After twelve days of soaking, a fine, white colored cotton was used for sieving. Filter paper was used to filter sieved solution to make 0.7L filtrate solution. Rotary evaporator was used to evaporate the solvent from the filtrate solution. The consistency of the final ethanol extract (28gm) of the leaves was semisolid. Then the extract was stored at 4°C before it was used.

Experimental Animals:

For the pharmacological investigation, 48 male and female Swiss albino mice weighed between 28 to 33 gm, were collected from animal Lab of ICDDR, Dhaka, Bangladesh. They were stored in standard polypropylene cages with controlled environmental conditions (55-65% relative humidity, 12 hours light/dark cycle and $24.0 \pm 2^\circ\text{C}$ temperature). Also sufficient amount of food and water were supplied all the time. Process of experiments where animals involved, were conducted in accordance to ethical guidelines of ICDDR, Dhaka, Bangladesh and approved by the Institutional Ethical Committee of ICDDR, Dhaka, Bangladesh.

Drugs and Chemicals:

Indomethacin and Loperamide were collected from Square pharmaceuticals Ltd., Bangladesh and Beximco pharmaceuticals Ltd., Bangladesh respectively. Analytical reagent grade chemicals were used in all cases.

Acute Toxicity Test:

The acute toxicity for ethanolic extracts of *Swietenia mahagony* leaves was determined in mice according to the method of Lorke, 1983 [16] with slight modifications. Mice were divided into four groups of four mice each. Different doses of extracts (200, 400, 800, 1600 and 3200 mg/kg p.o.) were administered intraperitoneally and observed all groups over a period of 48 hour for signs of acute toxicity. The number of deaths within this period was recorded.

Analgesic activity:

To evaluate analgesic property of *S. mahagony*, acetic acid-induced writhing method and formalin-induced hind paw-licking method were used.

Acetic Acid Induced Writhing Method:

The method of acetic acid-induced writhing test described by Ahmed et al was used to test analgesic activity of ethanolic leaf extract of *S. mahagony* [17]. Mice were divided into four groups consisting of four swiss albino mice in each. Group I labelled as control where vehicle (Saline water, 10 mL/kg body weight) was administered. In group II, Indomethacin was administered at the doses of 10 mg/kg which was used as a standard drug while group III and IV received the sample extract orally at two different doses (100 and 200 mg/kg). After 30 minutes, intraperitoneally administration of acetic acid solution (1%) was given to each group at a dose of 10 mL/kg body weight. Five minutes later, number of writhing were counted for each mouse of all groups for thirty minutes.

Percentage inhibition was calculated by: average writhes in the control group minus average writhes in the test group divided by average writhes in the control group multiplied by 100 [18].

Formalin induced hind paw-licking method

The test was performed using the method described by Hunskaar and Hole [19]. Mice were divided into four groups consisting of four in each group. Vehicle (Saline water, 10 mL/kg body weight) was administered in Group I labeled as control group and standard drug, Indomethacin was administered at the doses of 10 mg/kg in group II. In group III and IV, sample extract administered orally at two different doses (150 and 300 mg/kg). 20 μl of 5% formalin was injected into the dorsal surface of the right hind paw 60 min after administration of control, standard and test sample. 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 is referred to as the early phase and the period between 15 and 30 min as the late phase. Each mouse of all groups were observed individually for counting the number of licking they made in first 5 minutes and 20-30 minutes after the administration of formalin.

Anti-diarrheal property

Castor-oil induced diarrhea model:

Anti-diarrheal activity of the plant extract is determined by using the method described by Jebunnessa et al [20]. Sixteen mice were taken and divided into four groups. Vehicle (Saline water, 1 mL/kg body weight) was administered in Group I served as control while Group II was administered with the standard anti-diarrheal drug Loperamide at a dose of 5 mg/kg body weight. Crude leaf extracts were given to Group III and IV at the doses of 250 mg/kg and 500 mg/kg respectively. After one hour, castor oil was administered to all mice at a dose of 0.5ml/mice. All mice were kept in separate metabolic cages with a transparent plastic container beneath the cage to collect feces. Each mouse of all groups was observed individually for counting the number of feces for 5 hour.

Statistical analysis:

The data were presented as mean \pm SEM (n=4). Results were analysed by one way analysis of variance (ANOVA) followed by Dunnett's t-test. Probability (P) value of 0.05 or less ($P < 0.05$) was considered as significant. Here ^a $P \leq 0.001$, ^b $P \leq 0.01$ and ^c $P \leq 0.05$ compared to control.

III. RESULTS

Analgesic activity

Acetic acid induced writhing test:

In acetic acid-induced writhing test, the plant extract at a dose of 200 mg/kg significantly reduced the number of writhing. Standard drug, Indomethacin showed highest percentage of inhibition (77.19%) at the dose of 10 mg/kg body weight. A dose of 100 mg/kg of the extract showed no significant inhibition of acetic acid induced writhing.

TABLE 1. Evaluation of analgesic activity of ethanolic extract of *S. mahagony* by acetic acid induced writhing method.

Groups	Dose	No. of writhing Groups of mice				Average no. of Writhing ± SEM	% inhibition
		I	II	III	IV		
Control (saline)	10 ml/kg	27	32	30	25	28.5±3.11	-----
Indomethacin	10 mg / kg	7	9	4	6	6.5±2.08 ^a	77.19
Ethanolic extract of plant	100 mg/kg	19	21	17	25	20±3.41	28.07
	200 mg/kg	14	15	13	08	12.5±3.11 ^a	56.14

Values are mean ± SEM (n = 4). ^a P<0.001, ^b P<0.01 and ^c P<0.05 compared to control. One way analysis of variance (ANOVA) followed by Dunnett's *t*-test

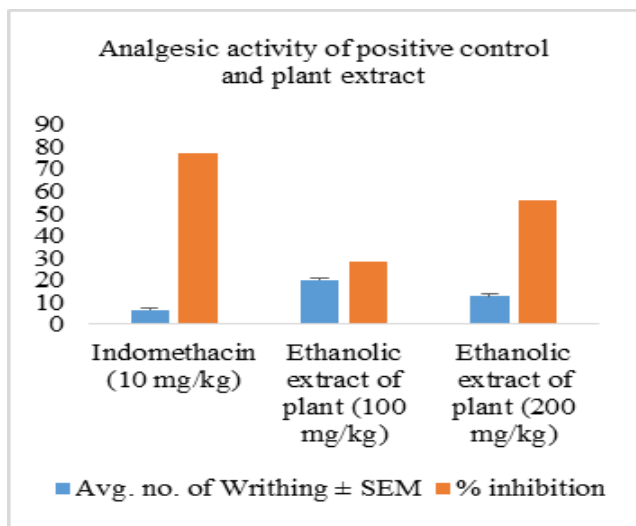


Fig. 1. Evaluation of % of inhibition of analgesic activity of extract of *S. mahagony* by acetic acid induced writhing method

Formalin induced hind paw-licking test:

In early and late phase of formalin induced hind paw licking test, the administration of standard drug, Indomethacin inhibited 76.92% and 58.14% licking response respectively which are statistically significant (^a P<0.001 and ^c P<0.05 respectively). The inhibition of licking response by ethanolic extract of *S. mahagony* was 23.85% at 150mg/kg dose and significant (^a P<0.001) inhibition of 43.08% was found at 300mg/kg dose during the early phase. In the late phase of formalin test, the administration of extract showed 23.26% inhibition at 150 mg/kg dose which is statistically significant (^c P<0.05) as compared to the control group and 34.88% inhibition at 300 mg/kg dose.

TABLE 2. Evaluation of analgesic activity of ethanolic extract of *S. mahagony* by formalin induced hind paw-licking method (early phase).

Groups	Dose	No. of Licking Groups of mice				Average no. of Licking ± SEM	% inhibition
		I	II	III	IV		
Control (saline)	10ml/kg	31	37	28	34	32.5±3.87	-----
Indomethacin	10mg / kg	5	9	6	10	7.5±2.38 ^a	76.92
Ethanolic extract of <i>S. mahagony</i>	150mg/kg	22	27	33	17	24.75±6.85	23.85
	300mg/kg	21	16	18	19	18.5±2.08 ^a	43.08

Values are mean ± SEM (n = 4). ^a P<0.001, ^b P<0.01 and ^c P<0.05 compared to control. One way analysis of variance (ANOVA) followed by Dunnett's *t*-test

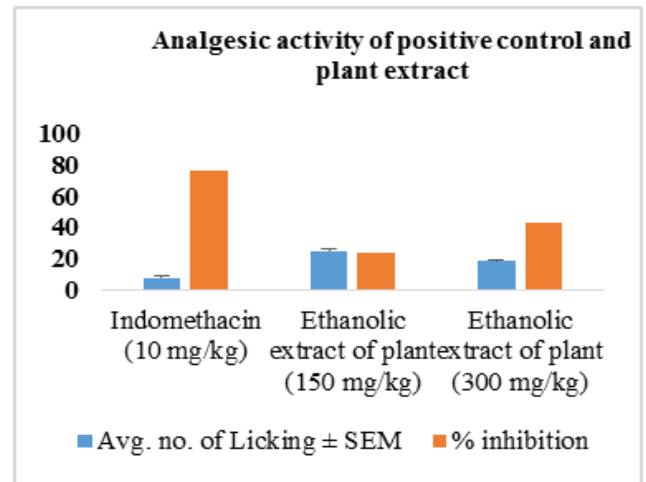


Fig. 2. Evaluation of % inhibition of ethanolic extract of *S. mahagony* by formalin induced hind paw-licking method (early phase).

TABLE 3. Evaluation of analgesic activity of ethanolic extract of *S. mahagony* by formalin induced hind paw-licking method (late phase).

Groups	Dose	No. of Licking Groups of mice				Average no. of Licking ± STD	% inhibition
		I	II	III	IV		
Control (saline)	10ml/kg	16	7	11	9	10.75±3.86	-
Indomethacin	10mg / kg	8	2	5	3	4.5±2.65 ^c	58.14
Ethanolic extract of <i>S. mahagony</i>	150mg/kg	11	9	5	8	8.25±2.5 ^c	23.26
	300mg/kg	5	8	10	5	7±2.45	34.88

Values are mean ± SEM (n = 4). ^a P<0.001, ^b P<0.01 and ^c P<0.05 compared to control. One way analysis of variance (ANOVA) followed by Dunnett's *t*-test.

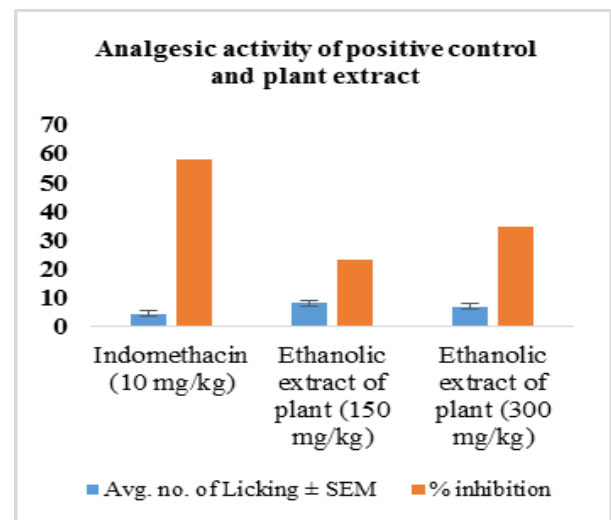


Fig. 3. Evaluation of % inhibition of ethanolic extract of *S. mahagony* by formalin induced hind paw-licking method (late phase).

Anti-diarrheal activity:

In the castor oil-induced diarrhea experiment, the 250 mg/kg extract of *S. mahagony* decreased number of defecation which was significant for soft and watery stool (^c P<0.05 and ^a P<0.001 for respectively) when compared to the control group and showed 88.89% inhibition of defecation. Likewise, 500 mg/kg showed 94.44% inhibition of defecation which was similar as standard control (Loperamide) and also reduced number of defecation which was significant for hard, soft and

watery stool (^b $P \leq 0.01$, ^a $P \leq 0.001$ and ^a $P \leq 0.001$ respectively) as compared to control group. Furthermore, Loperamide at a dose of 5 mg/kg decreased number of hard, soft and watery stool significantly (^a $P \leq 0.001$).

TABLE 4. Evaluation of antidiarrheal activity of ethanolic extract of *S. mahagony* by castor oil-induced diarrheal method.

Treatment	Number of Defecation			% inhibition of defecation
	Hard stool	Soft stool	Watery stool	
Normal control group (1 ml/kg)	5.25 ± 1.26	2.25 ± 0.5	4.5 ± 1.29	-
Standard control group (5 mg/kg)	1.5 ± 0.58 ^a	0.25 ± 0.5 ^a	0.25 ± 0.5 ^a	94.44
Ethanolic extract of <i>Swietenia mahagony</i> (250mg/kg)	3.75 ± 1.71	0.75 ± 0.96 ^c	0.5 ± 0.58 ^a	88.89
Ethanolic extract of <i>Swietenia mahagony</i> (500mg/kg)	2 ± 0.82 ^b	0.25 ± 0.5 ^a	0.25 ± 0.5 ^a	94.44

Values are mean ± SEM (n = 4). ^a $P \leq 0.001$, ^b $P \leq 0.01$ and ^c $P \leq 0.05$ compared to control. One way analysis of variance (ANOVA) followed by Dunnett's *t*-test.

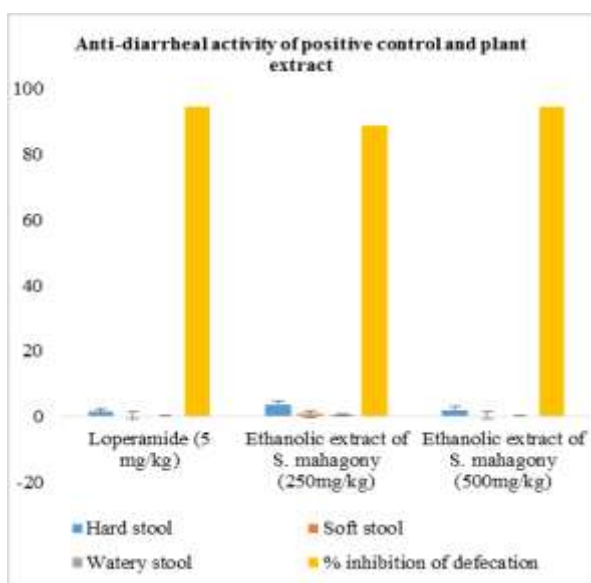


Fig. 4 Anti-diarrheal effects of ethanolic extract of *S. mahagony* leaves

IV. DISCUSSIONS

Unpleasant sensory and emotional experience associated with actual or potential tissue damage is officially defined as pain. It proactively warns signal against disturbances of the body [21]. Acetic acid causes pain and localized inflammation by the action of prostacyclines and prostaglandin-E (PG-E) production which cause a sensation of sharp localized pain by stimulating the Aδ-fibres. It also induces the increased level of PGE2 and PGF2α in the peritoneal fluid which is responsible for pain production. Various peripherally acting analgesic drugs such as ibuprofen, indomethacin, aspirin and diclofenac sodium have shown inhibition to acid induced writhing by inhibiting the synthesis of prostaglandin. Hence, analgesic effect of an agent can be defined by the reduction in the number of writhing through the inhibition of prostaglandin synthesis [22]. The ethanolic leaf extract of *S. mahagony* showed significant (^a $P < 0.001$) inhibition at 200 mg/kg dose as compared to control group which suggests that the reduction

of pain by the inhibition of prostaglandin synthesis may be due to the presence of analgesic properties in the extract.

The involvement of either central or peripheral activity can not be confirmed only with this test [23]. Therefore, formalin test is usually carried out along with acetic acid-induced writhing test to distinguish between peripheral and central pain. The formalin model was developed to assess pain and evaluate analgesic drugs in laboratory animals. In this test, pain-related behaviors are determined by two temporally distinct phases. In the first phase of pain, formalin has been reported to activate nociceptors and primary afferent fibers through the release of bradykinin and tracheykinins. In the second phase, histamine, serotonin, prostaglandin and excitatory amino acids are released due to an inflammatory reaction by tissue injury. The first phase is inhibited by opioid analgesics whereas the second phase is inhibited by non-steroidal anti-inflammatory drugs and opioid analgesics [24]. *S. mahagony* leaves showed maximum pain inhibition of 43.08% at 300mg/kg dose whereas Indomethacin showed 76.92% pain inhibition in early phase of formalin induced hind paw-licking method. In late phase, *S. mahagony* leaves showed 34.88% pain inhibition at 300 mg/kg dose whereas Indomethacin showed 58.14 % pain inhibition. The findings suggest that the plant extract not only inhibited the production of prostaglandin but also inhibited the activation of primary afferent fibers by formalin. The study findings showed that ethanolic extract of *S. mahagony* possess analgesic activity in the two analgesic models. The extract showed dose dependent inhibition with high doses of the extract showing a significant percentage of inhibition.

Diarrhea results from an imbalance between the absorptive and secretory mechanisms in the intestinal tract accompanied by quick resulting in an excess loss of fluid in the faeces. In some diarrhea the secretory component predominates while other diarrhea is characterized by hypermotility. For evaluating the antidiarrheal property of drugs, castor oil induced diarrhea model is commonly used. Diarrhea is caused by the active metabolite of castor oil which is called ricinoleic acid [25, 26] that stimulates peristaltic activity in the small intestine, leading to changes in the electrolyte permeability of the intestinal mucosa. This sequence of events leads to the release of prostaglandins which stimulates motility and secretion thus reduces the absorption of sodium and potassium ions [27].

The ethanolic leaf extract of *S. mahagony* showed significant antidiarrheal activity (94.44%) at 500 mg/kg dose which was similar to that of the standard drug loperamide (5 mg/kg). It is probable that the extracts were able to inhibit electrolyte permeability to the intestine through the inhibition of prostaglandin release. Accumulation of intestinal fluid is suppressed by the ethanolic extract of plant which might also inhibit gastrointestinal functions [27]. Membrane bound enzyme Na⁺ and K⁺ ATPase has been related to sodium and potassium transport in the intestine. During diarrheal conditions, Na⁺ and K⁺ ATPase are decreased which relates to an interruption in the normal water and electrolyte absorption. The activity of Na⁺ and K⁺ ATPase might be affected by the decrease of water along with Na⁺ accumulation. The stimulated fluid, Na⁺ and K⁺ secretion which are induced by

the castor oil were inhibited by the extracts in a dose dependent manner.

Earlier studies indicated that antidiarrheal properties of medicinal plants were mostly due to tannins, alkaloids, saponins, flavonoids, sterol and triterpenes [27]. The antidiarrheal property of the extract of *S. mahagony* found in the present study could be due to the presence of tannins, alkaloids, saponins, flavonoids, steroids in this plant [28-29].

V. CONCLUSION

In this current research work it was tried to evaluate the analgesic and antidiarrheal properties of *S. mahagony*. The results of this investigation shown that ethanolic extract of *S. mahagony* possessed significant analgesic and antidiarrheal properties. There is a need for a further research to be carried out to fractionate and purify the extract, in order to find out the constituents responsible for the analgesic and antidiarrheal activities of *S. mahagony*.

VI. ACKNOWLEDGEMENT

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VII. CONFLICT OF INTEREST STATEMENT

We declare that we have no conflict of interest.

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