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Antinociceptive Activity of Methanolic Leaf Extract of *Parthenium hysterophorus* L.

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Abstract: The present study was aimed to evaluate the antinociceptive property of *Parthenium hysterophorus* L. The central antinociceptive activity was analyzed by hot plate and tail immersion method; whereas acetic acid-induced writhing test and formalin induced licking tests were carried out for peripheral antinociceptive activity. The acute toxicity study revealed that methanol extract of the plant was moderately toxic at a dose of 500 mg/kg body weight. In hot plate method and tail immersion test the methanol extract exhibited significant analgesic activity ($P < 0.001$) at a dose of 2.5 and 5 mg/kg revealed its central antinociceptive activity. The significant activity ($p<0.01$) in acetic acid induced writhing test and formalin induced licking test implies the peripheral antinociceptive property of the extract at both doses. These findings justify that *P. hysterophorus* L. can be a valuable natural antinociceptive source which seemed to provide potential phytotherapeutics against various ailments.

Keywords: *Parthenium hysterophorus* L*;* antinociceptive*; morphine*

I. Introduction

Traditional herbal medicine is used as the primary source of treatment in majority of people in the developing world [1]. Almost one fourth of the prescribed drugs of all over the world are from plants and at least 119 chemicals derived from 90 plant species is considered as important drugs in at least one or more countries [2]. Moreover, due to availability, affordability and accessibility of medicinal plants led to their high demand and usage [3]. Secondary metabolites such as alkaloids, iridoids and phenolics generally produced by plants, especially for their defense mechanisms, have been implicated in the therapeutic properties of most medicinal plants [4].

Most analgesic drugs such as NSAIDs, COX-2 inhibitors and opioids exhibit an extensive range of adverse effects including gastrointestinal disorders, kidney problems and other unwanted effects. Drug regulatory authorities have been imposed a boxed warning on the label of some COX-2 selective inhibitor for cardiovascular and gastrointestinal risks [5].Nonsteroidal anti-inflammatory drugs (NSAIDs) are used to treat mild to moderate acute pain as well as exhibit anti-inflammatory effects by inhibiting the cyclooxygenase enzyme [6]. But, these drugs are effective in only 30% of patient and relieve only 50% of pain [7]. Also misuse and addition of opoids is a rising problem [8]. Besides most of traditional analgesics are less effective in neuropathic pain [9]. Therefore, to find out a safe and effective analgesic drugs with lesser side effects is still tough for the researchers and medicinal plants may become common source of therapeutically active chemical substances with fewer side effects [10].

Parthenium hysterophorus L. is also known as congress weed, carrot weed, star weed, white top, chatak chandani, bitter weed, ramphool and gajar grass [11], belongs to the family Asteraceae is a poisonous and problematic weed, is now posing a serious threat to crop cultivation and also to human and animal health. It is a noxious weed native to tropical America and several subtropical parts of the universe. The plant is currently vastly distributed in Indian, Africa, China, Vietnam, Pacific islands and Australia [12]. The plant is an annual, erect and profusely branched herb. Height varies between 50-150cm, stem highly branched; leaf simple with profusely dissected leaflets; flower heads occur on a corymb, phyllaries 10 in 2 series, ovate, dull white, 3-4mm in diameter; disc floret: numerous, dull white; stamen - 4, anther- exerted; ovary sterile; ray floret: found just opposite to inner phyllaries, only 5 ray florets per flower head, corolla obsolete, stamen-absent, stigma-parted, style short, ovary oval, dorsiventrally flattened. Fruit cypsela, each flower head bearing 5 cypsela, flat and triangular in shape with thin, white, spoon shaped appendages [13]. A typical mature plant can produce from 15000 to 25000 seeds [14, 15].
Rastogi and Mehrotra described *Parthenium hysterophorus* L. as a medicinal plant [16]. Traditionally, all parts of the plant are used as bitter tonic, febrifuge, emmenagogue, anti-dyscentric, and as an analgesic in neuralgia. The plant *P. hysterophorus* has antieosinophilic activity and also used to treat diabetes mellitus in Gujrat and Maharashtra [17, 18]. A decoction of root is used in treatment of amoeboitic dysentery [19]. Many scientists have also reported its use in the treatment of wounds, ulcerated sores, and fever, anemia and heart troubles [20].

Phytochemcials present in the leaves of *P. hysterophorus* have cytotoxic and antioxidant activity along with reasonable anti-HIV activity [21]. A poultice made from dried leaves used to treat bedsores and wounds and a range of skin disorders can be treated by the mixture of juice and oil or lime [22]. Also, the grandis of leaves have been reported to possess anti-periodic activity [23], fertility, fecundity and behavioral response [24]. Flower of the plant *P. hysterophorus* showed anti-cancer activity [25] and also the plant extract increased the survival of leukemic mice [26]. The plant has also been reported to possess activity against hepatic amoebiasis [27]. Many scientists have also reported the antimicrobial and antimycotic [28], antifungal [29], hypoglycemic [30] and antimicrobial spermicidal [31] potential of the plants.
Many plant species are affected by two allelochemicals sesquiterpene lactones and phenolics which are released from *Parthenium hysterophorus* [32]. Parthenin is the main sesquiterpene lactone while main phenolics are caffeic, vanillic, ferulic, chlorogenic and anisic acids [33,34,35], and both groups extensively decrease the seed germination and successive growth in many crops [36,37]. Mranda et al., reported that twenty seven compounds have been identified in the volatile oils take out from the plants *P. hysterophorus* where the major constituents are germacrene-D, trans-β-ocimene and β-myrcene and all the ingredients causes reduced seed germination and seedling vigor in lettuce [38]
The utilization of *P. hysterophorus* in several painful conditions in folk medicine and lack of scientific study reporting its antinociceptive activity in different animal models convinced use to assess the antinociceptive effect of methanol extract of *P. hysterophorus* in different peripheral and central pain models in mice.

II. **Materials and Methods**

II.1. Plant Materials

The leaves of *Parthenium hysterophorus* were collected during the month of January 2013 from Jahangirnagar University campus and the taxonomic authentication of the plant was done from Bangladesh National Herbarium institute, Mirpur, Dhaka (Accession no. 38686). The stem and other adulterants were removed at first. Then the leaves were washed with water to get the fresh sample. Then the collected samples were dried under shade at room temperature for five days. The dried materials were powdered using mixer and were used for solvent extraction.

II. 2. Extract Preparation.

150g of the dried powder was taken in a 500 ml beaker. Then methanol was added to the powder with continuous stirring until the powders were soaked properly. Then the mixer was continuously stirred

after few hours, and the beaker was kept for three days. At fourth day the extract was collected and filtered using a sterilized cotton filter. The volume of the extract was reduced by using “Rotary Evaporator”. Then this small volume of extract was dried at room temperature by normal air flow. After drying, 7.69g of dried extract was obtained from 150g of powder. The methanol extracts (MEPH) were then concentrated using rotary vacuum evaporator and were used for further studies.

II.3. Chemicals and Standard Drugs

Acetic acid, DMSO and methanol were purchased from Merck, Germany, and Morphine sulphate (standard) from Hameln Pharmaceuticals, diclofenac sodium was obtained from Square Pharmaceuticals Ltd. (Dhaka, Bangladesh). All other chemicals used were of analytical grade.

II.4. Animals

Swiss albino mice (20-25 g) were collected from Animal Resources Branch of the International Center for Diarrhoeal Disease Research, Bangladesh (icddr,b). The animals were kept in standard laboratory conditions (relative humidity 55-60%; room temperature 25 ± 2°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 prior to performing the experiments. The animals were fasted overnight before the 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. All experimental protocols were approved by the Ethics Committee of Stamford University Bangladesh (SUB/IAEC/13.04).

II.5. Drugs and Treatments

Morphine sulphate (5 mg/kg) was employed in hot plate, tail immersion tests and diclofenac sodium (10 mg/kg) was used in writhing, formaldehyde induced nociception as standard drug. These standard drugs were administered intraperitoneally 15 min before the experiments while the animals in control group received vehicle orally (DMSO) at the dose of 10 ml/kg body weight 30 min before the experiments. Methanolic extract was orally administered to the test animals 30 min before the experiments at the doses of 2.5 and 5 mg/kg body weight in both chemical and thermal pain models.

II.6. Phytochemical Screening

Standard procedures were followed for determining the presence of various phytochemicals such as alkaloids, steroids, flavonoids, reducing sugar, saponins, tanins, carbohydrates and resins in extract [39].

II.7. Acute toxicity studies

For assessing acute toxicity of the plant extract swiss albino mice were taken and divided into control and test groups each containing five animals. Methanolic extract of *P. hysterophorus* was administered at the doses of 250, 500 and 750 mg/kg. After gavages the animals were kept in separate stage and were allowed to food and water *ad libitum.* The animals were then observe for possible behavioral changes, allergic reactions (skin, rash, itching) and mortality for the left 72 hours [40].

II.8. Analgesic activity of methanol extract
II. 8. 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 ± 0.5°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 MEPH and were placed on Eddy’s hot plate kept at a temperature of 50 ± 0.5°C. A cut off period of 20

s was maintained to avoid paw tissue damage [41]. 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.

II. 8. 2. Tail immersion test

To evaluate the central analgesic property the tail flick test was performed. This procedure is based on the observation that morphine like drugs prolongs the tail withdrawal time from hot water in mice [42]. One to two cm of tail of the mice pretreated with morphine or MEPH were immersed in warm water kept constant at 54 ± 0.5°C. The latency between tail submersion and deflection of tail 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 morphine or MEPH.

II. 8.3. Acetic acid Induced writhing test

Acetic acid-induced writhing test was performed to evaluate the peripheral antinociceptive activity of MEPH in chemical-induced pain. The mice were treated with drug or MEPH 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 min after the injection of acetic acid, the mice were observed and the number of writhing was counted for 30 min [43]. The contractions of the abdomen, elongation of the body, twisting of the trunk and/or pelvis ending with the extension of the limbs were considered as complete writhing.

II. 8.4. Formalin Induced licking test

Mice were injected with 20 µl of a 2.5% formalin solution (0.92% formaldehyde) made up in saline into the subplantar region of the right hind paw 60 min after MEPH treatment and 15 min after injection of diclofenac sodium. Licking of the injected paw was recorded as nociceptive response from 0-5 min (neurogenic phase) and 15-30 min (inflammatory phase) after formalin injection [44-45].

II. 9. Statistical Analysis

The results are presented as MEAN ± SEM. The statistical analysis of the results was performed using one way analysis of variance (ANOVA) followed by Dunnett's post hoc test using SPSS 11.5 software. Differences between groups were considered significant at a level of $p < 0.001$ and $p < 0.05$. The results of the tail immersion and hot plate tests were given with percentage of the maximal possible effect (% MPE), which was calculated using the following formula.

% MPE = [(post drug latency) - (predrug latency) / (cut off latency) - (predrug latency)] ×100

III. Results

III.1. Phytochemical screening

The preliminary phytochemical screening of crude Methanolic extract of leaves of *Parthenium hysterophorus* reveals the presence of alkaloids, carbohydrates, resins, tannin, saponin, flavonoids, reducing suger and steroids.

III.2. Acute Toxicity Test

From the acute toxicity test it is observed that there was no mortality at dose 300 mg/kg but it showed mortality at dose 500 mg/kg and 750 mg/kg body weight. The calculated LD50 was 587.6 mg/kg body weight.

III.3. Analgesic activity

III.3.1. Hot plate test

The antinociceptive activity of MEPH and morphine are showed in Table1. Here MEPH showed significantly ($p>0.001$) increase the reaction time to the thermal stimulus. The standard drug Morphine showed highest latency during the observation period.

III.3.2.Tail immersion test.

The antinociceptive effect of MEPH and standard drug Morphine is summarized in Table 2. MEPH at both doses (2.5 and 5 mg/kg) significantly increased the latency period to hot-water induced thermal stimuli ($p<0.001$) in a dose dependent manner. Morphine showed highest latency, however, the extract also showed significant latency at 2.5 and 5 mg/kg doses ($p<0.001$) at different observation time.

III.3.3. Acetic acid induced licking test

A significant reduction was observed in the number of writhes induced by acetic acid after MEPH treatment in mice ($p<0.001$). It is clear from Table 3 that the antinociceptive activity of MEPH was dose dependent. The maximum pain relieving effects (41%) was given by 5 mg/kg treatment while diclofenac sodium (10 mg/kg) produced a stronger analgesic effect.

III.3.4. Formalin induced nociception

Oral administration of MEPH at the doses of 2.5 and 5 mg/kg significantly ($p<0.05$,$p<0.001$) reduced the formalin induced paw licking in late phases of the test (Table 4). Diclofenac sodium demonstrated complete inhibition of licking in late phase. MEPH showed a dose-dependent increase in the licking inhibition in both phases.

IV. Discussion

The presence of alkaloids, flavonoids, tannins, reducing sugars, resins, and steroids may contribute of some biological activity of methanolic extract of *Parthenium hysterophorus L*. Flavonoid compounds often reveal a wide range of pharmacological activities including analgesic and anti-inflammatory activities [46-48]. Among others terpenoid substances also reported to have these properties [49-50]. Such activity has been atributed to the ability to inhibit phosphaolipase A2 and thereby ultimately blocking the metabolism of arachidonic acid [51]. A number of alkaloids may also prevent inflammation through blocking the metabolic pathway of arachidonic acid [52-53].

There are two types of analgesics so far been isolated from plants either peripherally or centrally acting [54]. The present study revealed that MEPH has both peripheral and centrally acting analgesic activity. The hot plate test measures the complex feedback to a non-inflammatory acute nociceptive input and is one of the models normally used for central nocieceptive activity. The method is considered to be selective for centrally acting drugs, so any agent that causes a persistence of the hot plate latency must be centrally acting [55]. The methanolic extract of *Parthenium hysterophorus L*. showed a longer latency period than that of control group in a dose dependent manner in the hot plate test, which reveals that the extract has activity on central nervous system.

Tail flick method is also useful for the assessment of centrally acting analgesics which is known to increase the pain threshold of mice towards heat. In our current study we have found that the extract in both doses causes significant prolongation of the latency period. Both hot plate test and tail flick tests are handy to determine the involvement of the opioid receptors in the action of the narcotic drugs or other analgesic agents that give effect in this pathway [56].

For peripheral antinociceptive activity test acetic acid induced writhing test has been used over the years [57]. Moreover, this test is vastly established as a visceral pain model since there is involvement of the release of endogenous mediators of pain, such as prostaglandins, kinins, etc [58-59]. Oral administration of MEPH significantly reduce the writhing response. The extract of *Parthenium hysterophorus L* may act as an inhibitor of prostaglandin synthesis because the nociceptive

mechanism of abdominal writhing induced by acetic acid involves the release of arachidonic acid metabolites via cyclooxygenase (COX) and prostaglandin synthesis [60]. Besides various flavonoids also perform as antinociceptive and anti-inflammatory agents due to their ability to inhibit arachidonic acid metabolis [61-63]. Preliminary phytochemical screening of *P. hysterophorus L.* qualitatively identified the presence of flavonoids, phenolic compounds, tannins and saponins. So, flavonoids present in the plant might be responsible for antinociceptive activity.

On the other hand formalin test, another chemical induced method exhibits biphasic reaction comprising an neurogenic (early) and an inflammatory (late) phase reaction and originates mostly from neurogenic inflammation followed by participation of kinins and leukocytes with their pro-inflammatory factors including prostaglandins [64]. It is also accounted that formalin causes acute inflammation by causing cell injury which results the production of endogenous mediators [65].
Our findings reveals that the plant extracts at given doses produced antinociception against both neurogenic and inflammatory phase of formalin induction. The fact that the plant extract at tested doses produced analgesia in all nociceptive models in indicative that it possesses both central and peripheral antinociceptive effects and the mechanism of action of the extract could, in part, be relatd to lipooxygenase and/or cyclooxygenase of the arachidonic aicd cascade and/or opioid receptors.

Table 1: *Effect of methanolic extracts of P. hysterophorus in hot plate method.*

Treatment	**Dose**	**Response times (in seconds)**				
		Pretreatment	**30 min**	**60 min**	**90 min**	**120 min**
Control	10mL/kg	4.80±.267	5.31±0.393	7.24±0.275	7.53±0.180	8.76±0.170
Morphine	5 mg/kg	5.74±.268	9.49±0.373*	11.23±0.183*	13.95±.157*	15.73±0.466*
MEPH	2.5mg/kg	5.37±0.711*	7.21±0.152*	8.56±0.121*	9.49±0.220*	11.60±0.241*
MEPH	5mg/kg	6.68±0.441*	7.58±0.213*	8.67±0.523*	9.62±.237*	12.57±0.588*

Each value is presented as the mean ± SEM (n=5). MEPH= methanolic extract of *Parthenium hysterophorus.* *p < 0.001 compared with the control group (Dunnett's test).

Table 2: *Effects of methanolic extract of P. hysterophorus in tail immersion method*

Treatment	Dose	Response times (in seconds)				
		Pretreatment	30 min	60 min	90 min	120 min
Control	10mL/kg	1.18±0.34	1.64±0.08	2.75±0.20	2.89±.028	3.24±0.11
Morphine	5 mg/kg	1.28±0.13	4.39±0.04*	4.88±0.15*	5.94±0.18*	7.09±0.07*
MEPH	2.5 g/kg	1.17±0.08	2.75±0.12*	4.05±0.15*	4.68±0.14*	5.19±0.15
MEPH	5 mg/kg	1.15±0.02	2.87±0.20*	4.40±0.17*	4.96±0.12*	5.88±0.18*

Each value is presented as the mean ± SEM (n=5). MEPH= methanolic extract of *Parthenium hysterophorus.* *p < 0.001 compared with the control group (Dunnett's test).

Table 3: *Effect of methanolic extract of P. hysterophorus in acetic acid- induced abdominal writhing test.*

Treatment	Dose	Mean± SEM	% of Inhibition
Control	10mL/kg	54.80±0.604	--
Diclofenac Sodium	10 mg/kg	18.10±0.534*	66.97
MEPH	2.5mg/kg	36.40±0.367*	33.57
MEPH	5 mg/kg	32.00±0.274*	41

Each value is presented as mean ± SEM (n=5). MEPH= methanolic extract of *Parthenium hysterophorus.* *p < 0.001 compared with the control group (Dunnett's test).

Table 4*: Effect of methanolic extract of P.hysterophorus in formalin induced licking test*

Treatment	Dose	Licking time (sec) of the hind paw			
		Early Phase (0-5 min)	% Inhibition	Late Phase (15-25 min)	% Inhibition
Control	10mL/kg	117.20±4.56	--	51.60±3.90	--
Diclofenac Sodium	10 mg/kg	39.60±1.44**	66.21	5.3±1.2**	89.72
MEPH	2.5mg/kg	90.40±2.50	22.86	7.40±1.03*	85.65
MEPH	5 mg/kg	88.00±2.30	24.91	2.80±0.38**	94.57

Each value is presented as mean ± SEM (n=5). MEPH= methanolic extract of *Parthenium hysterophorus.* *p < 0.05, **p < 0.001 compared with the control group (Dunnett's test).

V. Conclusion

The results of the present study reveal that the methanolic extract of *P. hysterophorus L.* possesses remarkable antinociceptive activity. These data provides justifications to the traditional use of the plant in pain and inflammatory disorders. However, more researches are required to understand the exact mechanism of analgesic activities and to separate the active constituent(s) responsible for the observed pharmacological effects.

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