Original Article

Evaluation of analgesic and antipyretic activities of *Mahanimba* (*Melia azedarach* Linn.) leaf and root powder

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Abstract

Introduction: *Mahanimba* (*Melia azedarach* Linn.) is a deciduous tree of family Meliaceae and its root is mainly used in painful condition such as *Gridhrasi* (sciatica) in Ayurveda. Ethnomedicinal claims indicate that its leaves are used to treat fever, but its medicinal activities have not been proven by research. **Aim:** This study was aimed to evaluate the potential analgesic and antipyretic activities of *M. azedarach* L. leaf powder (MLP) and *M. azedarach* L. root powder (MRP). **Materials and Methods:** The root and leaves of *M. azedarach* were made into powder using guidelines mentioned in the Ayurvedic Pharmacopoeia of India. The analgesic activity of the test drugs was evaluated against acetic acid-induced writhing test in mice and radiant heat-induced pain in albino rats, and antipyretic activity was evaluated against Brewer's yeast-induced pyrexia using Charles Foster rats. **Results:** In acetic acid induced writhing in mice, the test drugs MRP (1.3mg/kg) exhibit insignificant reduction in writhing reflex while MLP (1.3mg/kg) did not show any significant effect in comparison to the control group. MRP showed mild-to-moderate insignificant increase in latency of withdrawal response at 60 (26.74%) and 120 min (27.25%), while MLP did not show central analgesic effect in radiant heat model in rats. MRP showed a significant reduction in rectal temperature after 3 and 6 h, while MLP-treated group showed significant reduction after 6 h. **Conclusion:** MRP has mild-to-moderate peripheral and central analgesic effects, while MLP has not shown significant analgesic effects in both the experimental models. MRP has more pronounced antipyretic effect compared to MLP.

Keywords: Analgesic, antipyretic, *Mahanimba*, *Melia azedarach*

Introduction

Mahanimba (*Melia azedarach* Linn.) of Meliaceae family is a moderate-sized, deciduous tree, distributed in the wild forest area in the sub-Himalayan tract, Rohilkhand, Dehradun, and Saharanpur forests; commonly cultivated almost throughout India.[1] Leaves are bipinnately or tripinnately compound; leaflets are ovate-lanceolate and serrate. Inflorescence are in axillary panicles cymes; flowers are lilac-bluish white and fragrant. Fruit is a sub-globose drupe greenish, turning to pale yellow when ripe; stone five-celled bony and shallowly furrowed.[2] As per Ayurveda, *Mahanimba* possesses *Tikta, Kashaya Rasa, Sheeta Veerya*, and *Ruksha Guna* properties.[3] Ethnomedically, the leaves and bark of this plant are being used by tribal people for treating leprosy, scrofula, and other skin diseases internally and externally.[4] The decoction of leaves is administered in treating hysteria and malarial fever. Leaves are also being administered for reducing body pain in the form of paste. Also, leaves and roots are used to treat worms by tribal people.[5] Traditionally, different parts such as leaf, flower, seed, fruit and young branches are used for the treatment of malaria, diabetes, cough, skin disease and so on. Experimental and clinical studies prove that it has antioxidant, antimicrobial, anti-inflammatory, cardioprotective, analgesic, anticancerous, antiulcerogenic, antipyretic, anti-plasmodial and male contraceptive properties.[6] In spite of the large number of pharmacological studies carried out worldwide on *Melia azedarach,* scrutiny of published articles showed that there is a need to investigate the analgesic and antipyretic activities of its leaf and root powder. As in tribal claims, its leaves are used to treat fever and root is mainly used to get

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relief from painful condition such as *Gridhrasi* (sciatica) in Ayurveda. The scientific evidence already established in case of ethnolic extract of leaf of *M. azedarach* significant for its activity.[7] Hence, the present study is aimed to find out whether leaf and root powder of *M. azedarach* exhibits antipyretic activity and to confirm its analgesic activity.

Materials and Methods

Collection of plant

The root and leaves were collected just before flowering in the month of February 2014 from Jamnagar by the scholar. The identification and confirmation of the sample was carried out by Botanist and a copy has been preserved for future reference at the herbarium of the Department of Pharmacognosy Laboratory, Institute for Postgraduate Teaching and Research in Ayurveda (IPGT and RA), Jamnagar (Phm: 6131/2014).

Animals

Charles Foster albino rats of both sexes weighing 200 ± 20 g and Swiss albino mice of both sexes weighing 30 ± 5 g were used for the experimentation. The rats and mice were obtained from the Animal House attached to the Pharmacology Laboratory of IPGT and RA.

Experiments were carried out in conformity with the Institutional Animal Ethics Committee (IAEC) after obtaining its permission (IAEC/16/2014/05) in accordance with the guidelines formulated by CPCSEA, India. Six rats and mice were housed in each cage made of polypropylene with stainless steel top grill. The animals were exposed to 12 h light and 12 h dark cycles with a relative humidity of 50% -70% and the ambient temperature was 22°C ± 3°C. All animals were kept on the same environmental conditions. The animals were given food and water *ad libitum*.

Drug derivation

Physical impurities such as small pebbles, sticks and dried grass were removed manually from the collected raw drug. It was shade dried, grinded in mixer individually and sifted through sieve number 200 to obtain a fine powder and was stored in an air-tight container.

Dose fixation and schedule

The human therapeutic dose mentioned in the Ayurvedic Pharmacopoeia of India for MLP and MRP is 10 g.[8] The dose for the rat and mice was calculated by extrapolating the human dose to animals (900 mg/kg for rats and 1.3 g/kg for mice) based on the body surface area ratio by referring to the standard tables of Paget and Barnes.[9] Distilled water was used as a vehicle. The powder was administered by making a stock solution in distilled water (1 ml/100 g body weight of the rats and mice) just before administration and was administered to animals orally with the help of a gastric catheter sleeved to syringe.

Analgesic activity

Acetic acid-induced writhing syndrome

Animals were randomly divided into three groups of six animals in each group. The first group received distilled water and served as control group. The second and third groups received a stock solution of MRP (1.3 g/kg, p.o.) and MLP (1.3 g/kg, p.o.), respectively. One hour after drug administration, 1% v/v of acetic acid at the dose of 1 ml/100 g body weight of mice was injected intraperitoneally. Each animal was placed individually under a glass jar for observation. Onset of writhing was noted down for each mouse. The number of abdominal contractions, trunk twist response and extension of hind limb were noted for the first 0–10, 11–20, and 21–30 min. Results were expressed as a percentage change in writhing response in comparison to the latency of onset.[10]

Radiant heat by hot plate-induced pain

Animals were randomly divided into four groups of six animals in each group. The first group received distilled water and served as control group. The second group was kept as a standard reference and treated orally with pentazocine (20 mg/kg, p.o.) mixed with water (100 mg/kg). The third and fourth groups received a stock solution of MRP (900 mg/kg, p.o.) and MLP (900 mg/kg, p.o.), respectively. Effect of the test drug on the latency of paw licking or jump response, which represents pain threshold, was measured in rats employing the procedure of incremental hot plate. The paw licking or jump response was observed with the help of the IITC Life Science incremental hot/cold plate. The temperature of incremental hot plate was fixed at 55°C ± 0.2°C. Initial reading was noted for each rat for paw licking or jump response. Then, the drug was administered 1 h before experimentation. After the administration of the drug, paw licking or jump response was again recorded at 30, 60, 120, 180 and 240 min.[11]

Antipyretic activity

Brewer's yeast-induced pyrexia method

The test conditions and grouping were similar to radiant heat by hot plate-induced pain as mentioned above. Animals were kept fast overnight, but were provided with drinking water. The next morning, the initial rectal temperature of all rats was recorded. Then, fever was induced by injecting suspension of 12.5% dried Brewer's yeast in normal saline subcutaneously at a dose of 1 ml/100 g body weight. After 1 h of induction of fever, the respective test dosage forms of drug were administered and distilled water was administered to the control group. The rectal temperature was recorded after 3 h, 6 h, and 9 h of drug administration. The difference between the actual rectal temperature and initial rectal temperature was registered for each time interval. The maximum reduction in rectal temperature in comparison to control group was recorded.[12]

Statistical analysis

The obtained data has been presented as mean ± standard error of mean and difference between the groups was statistically determined by student's 't' test for paired and unpaired data and one way ANOVA followed by Dunnet's multiple't' test to assess the statistical significance between the groups. The value $P < 0.05$ is considered as statistically significant. The level of significance was noted and interpreted accordingly.

Results

MRP and MLP showed a insignificant increase in latency of onset in abdominal writhing syndrome in mice compared to control group. Both the test drugs did not decrease the number of writhing in the first phase of acetic acid administration, i.e., 0-10 min, compared to control group. In the late phase, i.e., 11-20 (15.36%) and 21-30 min intervals (22.84%), MRP produced a insignificant decrease in writhing response, while MLP did not produce any significant effect in comparison to the control group [Table 1].

The effect of MRP and MLP on radiant heat-induced pain through hot plate model in albino rats demonstrated that MRP showed mild-to-moderate insignificant increase in the latency of withdrawal response at 60 min (26.74%) and 120 min (27.25%) compared to control group. MLP did not show any effect on latency of withdrawal in comparison to the control group. Standard drug pentazocine showed a significant increase in withdrawal response in compared to initial as well as the control group [Table 2].

MRP showed a significant reduction in rectal temperature after 3 h and 6 h, while it showed a insignificant decrease after 9 h in comparison to the control group. MLP also showed a significant reduction in rectal temperature after 6 h, while it showed a insignificant decrease after 3 h and 9 h in comparison to the control group [Table 3].

Table 1: Effect of test drugs on acetic acid-induced writhing syndrome in mice

Group	Latency of onset (s)	Number of writhing		
		0-10 min	11-20 min	21-30 min
Control	167.00±43.21	30.40±5.61	38.40±8.13	32.40±4.17
MRP	189.60±39.54	37.40±8.48	32.50±8.31	25.00±4.83
MLP	187.17±27.97	27.50±6.67	37.50±6.02	32.00±5.40

Data: Mean±SEM. MRP: *Mahanimba* root powder; MLP: *Mahanimba* leaf powder, SEM: Standard error of mean

Discussion

Writhing test is a chemical method used to induce pain of peripheral origin by the injection of irritant principles such as acetic acid in mice. Analgesic activity of the test compound is inferred from a decrease in the frequency of writhing. The manifestations of abdominal writhing in mice were arching of back, extension of hind limbs, and contraction of abdominal musculature. The writhing response is considered a reflexive test.[13] In general, acetic acid causes pain by liberating endogenous substances such as serotonin, histamine, prostaglandins (PGs), bradykinins and substance P. Local peritoneal receptors are postulated to be involved in the abdominal constriction response.[14] The method has also been associated with prostanoids in general, that is, increased levels of PGE_2 and PGF2α in peritoneal fluids as well as lipoxygenase products. In the present study, *M. azedarach* root produced a insignificant decrease in writhing response, while the leaf did not produce any effect in compared to the control group. The mild-to-moderate peripheral analgesic effect of MRP may due to the inhibition of endogenous substances such as serotonin, histamine, PGs, bradykinins, and substance P in experimental animals.

Thermal induced nociception indicates narcotic involvement. The ability of the drug to prolong the reaction latency to thermally induced pain by hot plate in rats further suggests central analgesic activity. Thermal nociceptive tests are sensitive to opioid μ-receptors.[15] MRP showed

Table 2: Effect of test drugs against radiant heat-induced pain in rats

Groups	Duration of latency of paw licking or jumping								
	Initial	30 min	Percentage change to initial	60 min	Percentage change to initial	120 min	Percentage change to initial	180 min	Percentage change to initial
Control	4.10±0.41	4.45±0.32	8.53↑	3.74±0.27	8.71↓	3.66±0.24	10.49↓	4.06±0.37	0.85↓
MRP	4.62±0.24	4.24±0.35	8.01↓	4.73±0.43	2.60↑	4.67±0.39	1.19↑	4.28±0.48	7.35↓
MLP	4.52±0.19	4.97±0.25	10.11↑	3.71±0.14	17.92↓	3.60±0.34	20.35↓	3.51±0.38	22.34↓
Standard	4.63±0.38	5.62±0.38	26.29↑	5.23±0.50@.*	12.95↑	5.67±0.32*	22.46↑	4.69±0.65	1.29↑

Data: Mean±SEM. @P<0.05 compared with initial (paired t-test); *P<0.05 compared with control group (unpaired t-test). ↓: Decrease, ↑: Increase, MRP: *Mahanimba* root powder, MLP: *Mahanimba* leaf powder, SEM: Standard error of mean

Table 3: Effect of test drugs on Brewer's yeast-induced pyrexia in rats

Groups	Increase in pyrexia (°C)					
	After 3 h	Percentage change	After 6 h	Percentage change	After 9 h	Percentage change
Control	0.53±0.26↑	1.24±0.60↑	0.83±0.23↑	2.04±0.53↑	0.92±0.12↑	2.11±0.29↑
MRP	0.82±0.53*↓	1.87±1.19*↓	1.14±0.31@↓	2.61±0.72@↓	0.12±0.39↑	1.20±1.54↓
MLP	0.67±0.18↓	1.52±0.42↓	0.98±0.17@↓	2.26±0.39@↓	0.53±0.67↓	0.28±0.90↑

Data: Mean±SEM. *P<0.05, @P<0.01 compared with control group (ANOVA followed by Dunnett's t-test). ↑: Increase, ↓: Decrease, MRP: *Mahanimba* root powder, MLP: *Mahanimba* leaf powder, SEM: Standard error of mean

mild-to-moderate central analgesic activity, while MLP-treated group did not show any central analgesic activity in experimental animals.

The mild-to-moderate increase in pain threshold produced by *M. azedarach* root in both the models suggests the involvement of central pain pathways. Pain is centrally modulated through a number of complex processes including opiate, dopaminergic descending noradrenergic and serotonergic systems.[16,17] The analgesic effect produced by the *M. azedarach* root may be activated through central mechanisms involving these receptor systems or through peripheral mechanisms involved in the inhibition of PGs, leukotrienes, and other endogenous substances that are key players in pain. The presence of flavonoids, glycosides, steroids and tannins in the plant extract may be responsible for the investigated activity, because it is well established that a wide range of bioactivities are dependable on these phytochemicals.[18-20]

Yeast-induced fever is a model for pathogenic fever. Yeast-induced fever is due to the release of inflammatory mediators such as cytokines, interleukin IL-1, IL-6, tumor necrosis factor (TNF) etc.and PGE_2 produced by cyclooxygenase within the hypothalamus, which is regarded as the principal downstream mediator of fever.[21] Antipyretic drugs reduce the elevated body temperature and are known to act centrally on the temperature regulation center in the brain or peripherally through vasodilatation and heat dissipation. They reset the hypothalamic thermostat and rapidly reduce fever by promoting heat loss by sweating and cutaneous vasodilatation. They also act by inhibiting the synthesis of PGE_2.[22] MRP-treated group showed a significant reduction in rectal temperature after 3 and 6 h, while MLP-treated group showed a significant reduction in rectal temperature after 6 h in comparison to the control group. MRP has a more pronounced effect in comparison to MLP. The leaf contains alkaloids, tannins, flavonoids and phenolic compounds.[23] Alkaloids such as bolidine have the ability to reduce the elevated temperature by inhibiting the PGE_2 synthesis.[24]

Similarly, flavonoids such as baicalin possess antipyretic effect by suppressing TNF-α.[25] Therefore, its antipyretic activity might be due to the flavonoids and/or the alkaloidal components of the plant. It indicates that both drugs have inhibitory action on PGE_2 synthesis. Further investigations may be required to classify the fundamental active constituents responsible for bioactivities as well as their mechanism.

Conclusion

MRP showed mild-to-moderate peripheral and central analgesic effects, while MLP did not show any effect against acetic acid-induced writhing syndrome and radiant heat by hot plate-induced pain at the studied dose levels in experimental animals. However, significant effect in yeast-induced pyrexia in rats suggest that both MRP and MLP have shown antipyretic activity at the studied dose levels. MRP has more pronounced antipyretic activity then to MLP.

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Conflicts of interest

There are no conflicts of interest.

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हिन्दी सारांश

महानिम्ब (मेलिया अजाडेरेक) के पत्र एवं जड़ चूर्ण की शूलहर और ज्वरहर गतिविधियों का मूल्यांकन

श्वेता वेकारिया, मुकेश नारिया, के. निष्ठेश्वर, बी. आर. पटेल

महानिम्ब मेलिएसी वर्ग का पर्णपाती पेड़ है और इसकी जड़ मुख्य रूप से गृध्रसी जैसी शूल प्रधान स्थिति में उपयोगी है। पारम्परिक रूप में इसके पत्ते ज्वर में उपयोग किए जाते है , परंतु इसकी औषधीय क्रियाओं का मूल्यांकन अन्वेषण द्वारा स्थापित नहीं किया गया है। अतः इसके पत्र एवं जड़ का शूलहर और ज्वरहर कर्म का परीक्षण करने के लिए प्रयोग किया गया | इस हेतु महानिम्ब के पत्र एवं जड़ का चूर्ण आयुर्वेदिक औषधकोष में वर्णित पद्धति के अनुसार किया गया। वर्तमान शोध द्रव्यों का शूलहर प्रभाव एसीटिक ऐसिड जनित व्रिथिंग टेस्ट तथा रेडिएंट हीट जनित शूल द्वारा चूहों पर किया गया। ज्वरहर प्रभाव को निर्धारित करने के लिये ब्रीवेर यीस्ट जन्य ज्वर का परीक्षण चार्लस फॉस्टर चूहों पर किया गया। महानिम्ब के जड़ के चूर्ण ने व्रिथिंग प्रभाव की संख्या में सांख्यिकीय दृष्टि से कमी नही दिखायी तथा महानिम्ब के पत्र चूर्ण ने भी नियंत्रित वर्ग की अपेक्षा कम परिणाम दिया। जड़ के चूर्ण ने सांख्यिकीय दृष्टि से नगण्य ऐसी अल्प से माध्यम वृद्धि विनिवर्तन प्रक्रिया 60 मिनट (26.74%) तथा 120 मिनट (27.25%) पर दी, जबकि महानिम्ब पत्र चूर्ण ने रेडिएंट हीट मॉडल में केंद्रीय एनाल्जेसिक प्रभाव नही दिया । महानिम्ब जड़ चूर्ण ने गुद तापमान मे 3 तथा 6 घंटे के पश्चात सार्थक कमी की तथा महानिम्ब पत्र चूर्ण ने 6 घंटे के पश्चात सार्थक कमी की। इससे यह निष्कर्ष निकाला गया कि महानिम्ब जड़ चूर्ण में अल्प से मध्यम परिधीय तथा केंद्रीय एनाल्जेसिक प्रभाव है तथा इसके पत्र चूर्ण में यह प्रभाव नही है। इसके उपरांत महानिम्ब जड़ के चूर्ण का ज्वरहर प्रभाव पत्र चूर्ण की अपेक्षा अधिक है।