

Effect of *Gmelina arborea* Roxb in experimentally induced inflammation and nociception

Yogesh A. Kulkarni, Ritesh Panjabi, Vishvas Patel, Aditi Tawade, Alok Gokhale

Department of Pharmacology, SPP-School of Pharmacy and Technology Management, SVKM's NMIMS University, Mumbai, India

ABSTRACT

Background: *Gmelina arborea* Roxb (Verbenaceae), also known as "Gambhari", is an important medicinal plant in the Ayurveda. There are no meticulous scientific reports on effect of the plant on inflammation and pain. **Objective:** To study the anti-inflammatory and anti-nociceptive properties of aqueous extracts (AE) and methanol extracts (ME) of *G. arborea*. **Materials and Methods:** The AE and ME of stem bark of *G. arborea* was prepared by cold maceration and Soxhlet extraction technique respectively. Anti-inflammatory activity was determined in Wistar albino rats in a model of acute plantar inflammation induced by carrageenan. The anti-nociceptive activity was evaluated by using hot plate test and writhing test in Swiss albino mice. Significant differences between the experimental groups were assessed by analysis of variance. **Results:** AE and ME at dose of 500 mg/kg showed maximum inhibition in carrageenan induced inflammation up to 30.15 and 31.21% respectively. In hot plate test, the AE and ME showed the maximum response of 8.8 ± 0.97 ($P < 0.01$) and 8.2 ± 1.24 ($P < 0.01$) respectively at dose of 500 mg/kg when compared with control. AE showed maximum inhibition of writhing response (84.3%) as compared to ME (77.9%) in writhing test at a dose of 500 mg/kg. **Conclusion:** The findings suggested that *G. arborea* possess significant anti-inflammatory and anti-nociceptive activities.

Key words: Analgesic, anti-nociceptive, *Gmelina arborea*, hot plate test, rat paw edema, writhing test

INTRODUCTION

Gmelina arborea Roxb (Verbenaceae) is a well-known medicinal plant in the Ayurveda, an ancient Indian system of medicine. The roots, leaves, flowers, fruits and bark are used for treating different ailments in traditional medicine. The literature suggests use of the plant in treatment of scorpion sting, snake-bites,^[1] and diabetes.^[2] The plant is anthelmintic and used for treating hallucinations, excess thirst, piles, abdominal pains, burning sensations, and fever.^[3]

Address for correspondence:

Dr. Yogesh A. Kulkarni, SPP-School of Pharmacy and Technology Management, SVKM's NMIMS University, V.L. Mehta Road, Vile Parle (W), Mumbai - 400 056, India.

E-mail: yogeshkulkarni101@yahoo.com

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There are reports on phytoconstituents present in different parts of the plant. The isolation of luteolin^[4] and indole alkaloids^[5] from the leaves has been reported. Hentriacontanol^[6] and lignans such as arboreol, isoarboreol, methyl arboreol, arborone, gmelanone, gummadiol, and 7-oxodihydrogmelinol^[7-9] have been isolated from heartwood of the plant. Few coumarin glycosides^[10] and iridoid glycosides^[11] have been reported in roots and leaves, respectively. Three iridoid glycosides 6-O-(3'-O-benzoyl)- α -L-rhamnopyranosylcatalpol, 6-O-(3'-O-trans-cinnamoyl)- α -L-rhamnopyranosylcatalpol and 6-O-(3'-O-cis-cinnamoyl)- α -L-rhamnopyranosylcatalpol were isolated from aerial parts of *G. arborea* and structures were elucidated by spectral analysis.^[12]

The bark of the plant indicated presence of tyrosol [2-(4-hydroxyphenyl) ethanol]; (+)-balanophonin, an 8-5' neolignan, gmelinol, phenylethanoid glycoside {(-)-*p*-hydroxyphenylethyl [5'-O-(3,4-dimethoxycinnamoyl)-*b*-D-apiofuranosyl (1^{''} \rightarrow 6^{''})]-*b*-D-glucopyranoside}, 2,6-dimethoxy-*p*-benzoquinone and 3,4,5-trimethoxyphenol.^[13]

Crude extracts of the plant are reported to possess wound-healing properties,^[14] antidiarrheal activity,^[15] antioxidant activity,^[16] antidiabetic activity,^[17,18] and antiulcer activity.^[19] Toxicity studies of aqueous extract (AE) and

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methanol extracts (ME) have been reported by Kulkarni and Addepalli.^[20,21]

However, little information is available on the effects of *G. arborea* on inflammation and nociception. Therefore, the present study was designed to examine the effects of AE and ME of *G. arborea* bark, as it is mainly used in Ayurveda.

MATERIALS AND METHODS

Plant material

The bark of the *G. arborea* was collected from Jawhar District-Thane), Maharashtra, India in the month of November. Identification and authentication of the bark was carried out by Dr. P. S. N. Rao, Botanical Survey of India, Pune, India. A voucher specimen (b-03) of the bark is deposited in department for future reference. The bark after drying at room temperature was grounded into a fine powder. The powdered bark was used to prepare the AE and ME.

Preparation of aqueous extract

Cold maceration technique was used to prepare AE of bark of *G. arborea* (AE). Powdered bark (100 g) was macerated with 1 L of distilled water for 7 days, with occasional shaking. After 7 days, the AE was filtered and the marc was again subjected to maceration with distilled water for complete extraction. After filtration the AEs were combined and concentrated with the help of rotary vacuum evaporator under reduced pressure. The AE was dried in vacuum dryer and stored at -20°C until used. The yield of the AE was found to be 20% w/w, with respect to powdered bark. The extract was prepared freshly in double distilled water at the time of administration to experimental animals.

Preparation of methanol extract

Soxhlet extraction technique was used to prepare ME of bark of *G. arborea* (ME). One hundred gram of powdered bark was packed in soxhlet extractor and extracted with methanol. After complete extraction, the ME was filtered and concentrated under reduced pressure by using rotary vacuum evaporator. The ME was dried in vacuum dryer and stored at -20°C until used. The yield of the ME was found to be 28% w/w with respect to powdered bark. The extract was prepared freshly in double distilled water at the time of administration to experimental animals.

Preliminary phytochemical screening

Preliminary phytochemical screening of the aqueous and ME was done to identify presence of diverse phytoconstituents by standard methods.^[22]

Experimental animals

Wistar albino rats and Swiss albino mice were purchased from Haffkine Institute, Mumbai, India. The animals were

maintained in polypropylene cages in the Animal Facility with 12 hours light: 12 hours dark cycle. All the animals were kept under laboratory conditions (temperature 25°C ± 2°C, relative humidity 75% ± 5%) for an acclimatization period of 7 days before carrying out the experiments. Standard pellet diet (Nutrimix Laboratory Animal Feed, Maharashtra, India) and filtered water was provided *ad libitum* to all experimental animals. All the experimental protocols were approved by the Institutional Animal Ethics Committee (IAEC) constituted as per the norms of committee for the purpose of control and supervision of experiments on animals, India. All experimental procedures were performed according to the National Institutes of Health (NIH) guide for the care and use of laboratory animals.

Selection of doses

One tenth and 1/20th of the safe dose of the extracts were selected for the study.^[20,21] The extracts were prepared in double distilled water at the time of administration. The volume of extract administered to the experimental animals was not greater than 2 ml/100 g.

Anti-inflammatory activity

Pedal inflammation in male Wistar rats (120-150 g) was produced according to the method described earlier.^[23,24] An injection (*s.c.*) was made of 0.1 ml of 1% carrageenan into the right paw of each rat under the subplantar aponeurosis. The test groups were administered two doses of 250 and 500 mg/kg of both AE and ME, 1 hour before carrageenan injection. At the same time, the control group received 2 ml/kg distilled water and the reference group received 75 mg/kg phenylbutazone (*p.o.*). The paw volume was measured upto 6 hours after the injection of the edematogenic agent using a plethysmometer (IITC, USA).

Percentage reduction in edema volume was calculated by using the formula,

$$\% \text{ Reduction in paw volume} = \frac{V_0 - V_t \times 100}{V_0}$$

Where, V_0 = Volume of the paw of control at time 't',
 V_t = Volume of the paw of drug treated at time 't'.

Antinociceptive activity

To evaluate the anti-nociceptive activity of AE and ME, the effects of their treatments were assessed on two important experimental models: Hot plate test and writhing test.

Hot plate test

The hot-plate test was carried out as previously described.^[25] Swiss albino mice (25-30 g) of either

sex were fasted overnight with water given *ad libitum*. A hot-plate apparatus (IITC, USA) was used for determining the anti-nociceptive effect of the selected extracts. The animals were placed on the functioning hot plate ($54^{\circ}\text{C} \pm 1^{\circ}\text{C}$) to determine baseline responsiveness. The time elapsed until the animal licked one of its hind paws or jumped was recorded (latency time, in seconds). Mice that presented baseline reaction of more than 15 seconds were eliminated from the test. After the baseline responsiveness determination the animals were divided into six groups. Group I (Control) received distilled water, Group II and III received AE at dose of 250 and 500 mg/kg, group IV and V received ME at dose of 250 and 500 mg/kg and group VI received pentazocine (17 mg/kg). After administration of doses the latency to lick one of the hind paws or to jump off plate was determined at 15, 30, 45 and 60 min. A cut off period of 15 seconds is observed to avoid the damage to paws. Maximum possible effect (MPE) was calculated by the formula:

$$\text{MPE (\%)} = \frac{100 \times (\text{posttreatment latency} - \text{pretreatment latency})}{(\text{cut off time} - \text{pretreatment latency})}$$

Writhing test

The writhing test in mice was carried out using the method of Koster.^[26] The writhes were induced by 0.1 ml of intraperitoneal injection of 0.6% acetic acid (v/v). Group I (Control) received distilled water, Group II and III received AE at dose of 250 and 500 mg/kg respectively, the animals of group IV and V had ME at the same doses and group VI was administered standard drug (acetyl salicylic acid; 30 mg/kg), 45 min before an intraperitoneal injection of acetic acid. The number of muscular contractions was counted over a period of 20 min after acetic acid injection. The data represent the total number of writhes observed during 20 min and is expressed as writhing numbers.

$$\% \text{ Inhibition} = \frac{\text{Mean number of writhes (Control)} - \text{Mean number of writhes (Test)}}{\text{Mean number of writhes (Control)}} \times 100$$

Statistical analysis

The differences among experimental and control groups were determined using the statistical software Sigmasat Ver. 2.03 for Windows. Significant differences between the experimental groups were assessed by analysis of variance. All data are expressed as mean \pm standard error of mean (SEM); *P* value less than 0.05 was considered to be significant.

RESULTS

Preliminary phytochemical screening

The results of the preliminary phytochemical screening are presented in Table 1.

Anti-inflammatory activity

Subplantar injections of carrageenan provoked marked, time-related increase in the hind paw diameters of the 'untreated' control rats. Maximal swelling and/or edema occurred approximately 90 min following carrageenan administration. Table 2 shows effect of AE and ME in carrageenan induced rat paw edema. AE and ME showed significant reduction in paw volume when compared with control. AE at dose of 250 and 500 mg/kg showed maximum decrease of paw volume: 1.35 ± 0.04 ($P < 0.05$) and 1.32 ± 0.03 respectively when compared with control at 2 hours. ME at 500 mg/kg showed maximum decrease in paw volume 1.30 ± 0.03 ($P < 0.05$) as compared with control (1.89 ± 0.01) after 2 hours. The animals treated with AE and ME showed maximum reduction of 30.15% and 31.21% respectively, at 2 hours.

Anti-nociceptive activity

The effect of aqueous and ME of *G. arborea* was studied in hot plate test and acetic acid induced writhing method.

There was significant increase in pain threshold in mice towards the thermal stimuli by hot plate, after treatment with the two extracts [Table 3]. The time for paw licking response showed significant increase at 15, 30 and 45 min after treatment with AE and ME at doses of 250, 500 mg/kg. AE showed increase in paw licking response of 7.4 ± 1.16 ($P < 0.05$) and 8.8 ± 0.97 ($P < 0.01$) when compared with response before treatment at dose of 250 and 500 mg/kg respectively after 30 min of administration. ME at dose of 500 mg/kg exhibited significant increase ($P < 0.01$) in paw licking response after 30 min of administration. AE and ME showed maximum effect at 30 min at dose of 500 mg/kg.

The effects of AE, ME and acetyl salicylic acid on acetic acid induced writhing are presented in Table 4. All doses

Table 1: Preliminary phytochemical screening of *Gmelina arborea* extracts

| Type of constituent | Aqueous | Methanol |
|---------------------|---------|----------|
| Steroids | - | - |
| Carbohydrates | + | - |
| Alkaloids | + | + |
| Saponins | + | + |
| Glycosides | - | - |
| Flavonoids | - | - |
| Phenolics | + | + |
| Proteins | - | - |
| Amino acids | - | - |

+Indicates present, -Indicates absent

Table 2: Effect of aqueous and methanolic extracts of *Gmelina arborea* on carrageenan induced rat paw edema

| Group | Paw volume (ml) | | | | |
|---------------------------|-----------------|--------------------|--------------------|---------------------|---------------------|
| | 0 h | 1 h | 2 h | 4 h | 6 h |
| Control | 1.39±0.01 | 1.58±0.02 | 1.89±0.01 | 1.60±0.01 | 1.08±0.01 |
| AE (250 mg/kg) | 1.42±0.01 | 1.49±0.03 (5.69) | 1.35±0.04* (28.57) | 1.21±0.04* (24.37) | 1.05±0.03 (2.77) |
| AE (500 mg/kg) | 1.41±0.02 | 1.40±0.03* (11.39) | 1.32±0.03* (30.15) | 1.18±0.02* (26.25) | 1.01±0.04* (6.48) |
| ME (250 mg/kg) | 1.40±0.02 | 1.45±0.02* (8.22) | 1.38±0.04* (26.98) | 1.20±0.04* (25.00) | 1.02±0.03 (5.55) |
| ME (500 mg/kg) | 1.39±0.01 | 1.39±0.04* (12.02) | 1.30±0.03* (31.21) | 1.15±0.06* (28.12) | 0.98±0.07* (9.25) |
| Phenylbutazone (75 mg/kg) | 1.36±0.03 | 1.30±0.02* (17.72) | 1.18±0.03* (37.56) | 0.89±0.04** (44.37) | 0.62±0.05** (42.59) |

Values are expressed as mean±SEM (n=5), *P<0.05, **P<0.01 versus control, Figures in parentheses indicate the % inhibition, AE=Aqueous extracts, ME=Methanol extracts

Table 3: Antinociceptive effect of *Gmelina arborea* extracts in hot plate test

| Group | Paw licking response | | | | |
|------------------------|----------------------|--------------------|----------------------|----------------------|--------------------|
| | Basal | 15 min | 30 min | 45 min | 60 min |
| Control | 5.0±0.31 | 5.6±0.51 | 5.6±0.40 | 5.2±0.37 | 4.8±0.37 |
| AE (250 mg/kg) | 4.6±1.09 | 5.9±0.89 (12.5) | 7.4±1.16* (26.92) | 5.6±1.16 (9.61) | 4.6±1.16 (0) |
| AE (500 mg/kg) | 4.6±0.74 | 6.0±1.30* (13.46) | 8.8±0.97** (40.38) | 8.2±1.36** (34.61) | 4.8±0.66 (1.92) |
| ME (250 mg/kg) | 5.1±0.49 | 6.2±1.15* (11.11) | 6.8±1.15* (17.17) | 5.8±1.36 (7.07) | 4.8±0.37 |
| ME (500 mg/kg) | 5.0±0.91 | 7.2±1.42* (22.00) | 8.2±1.24** (32.00) | 7.8±1.74** (28.00) | 4.2±0.58 |
| Pentazocine (17 mg/kg) | 5.0±0.54 | 8.8±0.73** (38.00) | 11.2±0.58*** (62.00) | 13.0±0.89*** (80.00) | 14±0.20*** (90.00) |

Values are expressed as mean±SEM (n=5), *P<0.05, **P<0.01, ***P<0.001 versus control, Figures in parentheses indicate the % maximum possible effect, AE=Aqueous extracts, ME=Methanol extracts

Table 4: Effects of oral administration of *Gmelina arborea* extracts on acetic acid-induced writhing in mice

| Group | No. of writhes | % Inhibition |
|----------------------------------|----------------|--------------|
| Control | 25.4±0.81 | - |
| AE (250 mg/kg) | 6.4±0.93*** | 74.8 |
| AE (500 mg/kg) | 4.0±0.32*** | 84.3 |
| ME (250 mg/kg) | 7.6±0.81*** | 70.0 |
| ME (500 mg/kg) | 5.6±0.51*** | 77.9 |
| Acetyl salicylic acid (30 mg/kg) | 4.8±0.73*** | 81.1 |

Values are expressed as mean±SEM (n=5), ***P<0.001 versus control, AE=Aqueous extracts, ME=Methanol extracts

of the selected extracts (AE and ME) reduced acetic acid-induced writhing significantly. AE at dose of 250 and 500 mg/kg significantly ($P < 0.001$) reduced the number of writhings to 6.4 ± 0.93 and 4.0 ± 0.32 when compared with control (25.4 ± 0.81).

The AE at 500 mg/kg showed maximum inhibition of writhes (84.3%) which was more than the standard drug-acetyl salicylic acid (81.1%). ME showed significant reduction ($P < 0.001$) in writhings at doses of 250 and 500 mg/kg. The ME showed significant inhibition of 70% and 77.9% at dose of 250 and 500 mg/kg respectively.

DISCUSSION

Edema formation due to carrageenan in the rat paw is the biphasic event. The initial phase is attributed to the release of histamine and serotonin. The second phase of edema is due to the release of prostaglandins, protease and lysosome.^[27,28]

The second phase is sensitive to most clinically effective anti-inflammatory drugs.^[27,29] The edema produced after injection of carrageenan in rodents is associated with the production of several inflammatory mediators, such as bradykinin, nitric oxide, prostaglandins and cytokines.^[29-33] It has been found that the injection of carrageenan into the rat paw induces the liberation of bradykinin, which later induces the biosynthesis of prostaglandin and other autacoids, which are responsible for the formation of the inflammatory exudates.^[34] Therefore, it is suggested that the mechanism of anti-inflammatory action of *G. arborea* extracts may be related to inhibition of prostaglandin and other autocoids.

In hot plate test pain induced by thermal stimulus is specific for centrally mediated nociception^[35] and thought to involve opioids.^[36] The hot plate test was selected to examine a central analgesic activity, because it had several advantages, particularly its sensitivity to strong analgesics and limited tissue damage. Maximum effect of the plant extracts at all doses was reached at 30 min. The higher dose (500 mg/kg) of the AE and ME prolonged the hot-plate latency with time, which was less potent as compared to pentazocine. The ability of the extracts to prolong the reaction latency suggests that the extracts have a central analgesic activity.

The writhing response by acetic acid consists of a contraction of the abdominal muscle together with a stretching of the hind limbs which perceives peripheral analgesia.^[37] The test is unable to distinguish between central and peripheral analgesia.^[38] Still this is a very sensitive method used to screen anti-nociceptive activity for compounds than other

methods like tail flick test.^[39] The effects were comparable to that of the standard drug acetyl salicylic acid. The acetic acid induced abdominal constrictions are associated with sensitization of nociceptive receptors to prostaglandins.^[40] Thus we can predict that the anti-nociceptive effect of the selected extracts may therefore be due to its action on visceral receptors perceptible to acetic acid. The possible mechanism may also be linked to the inhibition of the production or action of prostaglandins.

Both extracts of *G. arborea* have shown presence of alkaloids and saponins which may be the possible chemical constituents responsible for its anti-inflammatory and anti-nociceptive activity.

CONCLUSION

The results obtained in the present study strongly suggest that *G. arborea* possesses significant anti-inflammatory and anti-nociceptive activities. The specific mechanisms through which AE and ME exerts their actions, as well as the specific bioactive compounds present in these extracts responsible for the activities, are currently under investigation.

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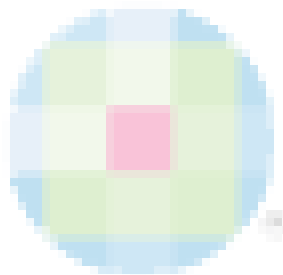
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Kulkarni, *et al.*: *Gmelina arborea* against inflammation and nociception

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- If the reference is correct for its bibliographic elements and punctuations, it will be shown as CORRECT and a link to the correct article in PubMed will be given.
- If any of the bibliographic elements are missing, incorrect or extra (such as issue number), it will be shown as INCORRECT and link to possible articles in PubMed will be given.