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Research Article

Evaluation of analgesic activity of *Aegle marmelos* steam bark in experimental animals

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ABSTRACT

Background: Alleviation of pain has always remained a prime concern of medicine. Numbers of anti-inflammatory and analgesic drugs like aspirin, indomethacin, phenylbutazone etc. are in practice, but because of their side effects, there is extensive search for new drugs and molecules with fewer side effects. Search for newer anti-inflammatory and analgesic agents having better or at least equal efficacy with minimal side effects is continuing throughout the world. Therefore, the search should continue and it is felt that herbal medicine has still a lot in store. Aegle marmelos is one of the most frequently used plant in the traditional and folklore systems of medicine and in religious rituals. Various activities of different parts like roots, leaves, flowers, fruits and seeds of AM were evaluated. It has analgesic, anti-inflammatory, antipyretic, antidiabetic, antioxidant, hepatoprotective and many other activities.
Methods: Analgesic activities of AMSBAE (50,100 and 200 mg/kg p.o.) were studied using tail flick test and acetic acid-induced writhes in rats and mice respectively.
Results: AMSBAE produces dose dependent analgesic activity in the tail flick test and acetic acid-induced writhing in mice ($P<0.05$).
Conclusions: AMSBAE has analgesic activity. The analgesic activity of AMSBAE was comparable to that of tramadol and Aspirin. Hence, AMSBAE could be a possible alternative to NSAIDs.

Keywords: Aegle marmelos, AMSBAE, Analgesia, Tail flick method, Writhes

INTRODUCTION

Pain is the body's defense and protective mechanism to withdraw from a painful stimulus.

The International Association for the Study of Pain (IASP) has defined pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage."[1]

Numbers of drugs are available in market to treat inflammation and pain, like non-steroidal anti-inflammatory drugs (NSADIs) and Opioids. Synthetic substitutes have no doubt taken over, but none of the anti-

inflammatory and analgesic drugs available today can be considered ideal, for their toxic effects. There is extensive search going on for new drugs and molecules with fewer side effects and there is lot of scope for herbal medicine in this view.

Aegle marmelos (AM) belongs to family Rutaceae, is commonly known as Bael. It is an important aromatic medicinal tree of Indian origin. The Bael is one of the sacred trees of the Hindus. It is used in the worship of Lord Shiva since mythology even till today.

Leaves, fruit, stem and roots of this tree at all stages of growth and development are used as ethno medicine against various human ailments.[2,3]

In Ayurvedic medicine, AM is used in various conditions like diarrhoea, dysentery, fever, jaundice, inflammation, ophthalmic conditions.[4] In Unani system of medicine, AM is used as haemostatic, astringent and aphrodisiac agent. It is used as a tonic for heart, brain and GIT.[4]

Various activities of different parts like roots, leaves, flowers, fruits and seeds of AM were evaluated. They possess analgesic, anti-inflammatory, antipyretic, antidiabetic, antioxidant, hepatoprotective and many other activities. Decoction of AM roots, root bark and stem bark is used to cure palpitations, abdominal pain, fever, urinary troubles and melancholia.[5]

After the search of literature on analgesic activity, it was found that various parts like leaves, roots, fruits, etc., with different types of extracts were studied frequently by researchers. As compared to these parts, studies on stem bark are very less.

Hence, in the present study, here is an attempt to evaluate the analgesic effects of AM stem bark aqueous extract (AMSBAE) in experimental animals. The objective of this study was to evaluate analgesic activity of AMSBAE in experimental animals.

METHODS

Approval of institutional animal ethics committee was obtained before commencing the study. Experiments were conducted as per guidelines of committee for the purpose of control and supervision on experiments on animals (CPCSEA). It was carried out in research laboratory, department of pharmacology, Dr. Panjabrao Deshmukh Memorial Medical College, Amravati, Maharashtra, India. Duration of study was 4 months.

Material

Collection of parts of plant and its authentication

The stem bark of AM was collected from the Botanical garden of Ayurvedic College, in the city, in the month of November and December. Botanical identity of plant was confirmed and authenticated by taxonomist.

Animals

Both albino rats and mice were procured from central animal house of our institute. Animals were kept seven days for adaptation before subjecting to experiments. The rats and mice were grouped in separate cages with six animals in each cage. They were maintained in a colony room at ambient temperature of 23±1°C with help of air coolers and enough humidity on a 12 hour light-dark cycle. They had free access to food and water. Similar conditions were provided in laboratory while performing experiments. Study was conducted during the day time (between 10.00 to 18.00 hours).

30 Albino rats of either sex, weighing 150-250 gm and 30 Albino mice of either sex, weighing 25-30 gm were used for tail flick and acetic acid induced writhes method respectively.

Drugs and chemicals

Aspirin, tramadol, 1% acetic acid, AMSBAE, doubly distilled water, normal saline (NS 0.9%)

Preparation of plant extract (decoction)[6]

The collected stem bark pieces were carefully cleaned with tap water, dried under shade, powdered in electric grinder. 1 gm of fine powder of stem bark was boiled in 16 ml double distilled water till volume was reduced to 4 ml. It was centrifuged and filtered through filter paper. Fresh decoction was used every time.

Acute toxicity study[7]

Acute oral toxicity [up and down procedure (UDP)] study for the test extract of *Aegle marmelos* plant was carried out using OECD/OCED (organisation for economic co-operation and development) guidelines 425. Test procedure minimizes the number of animals required to estimate the oral acute toxicity. Healthy, young female albino rats weighing 150-200 gm were taken.

Limit test at 2000 mg/Kg[7]

A test drug at a dose (AMSBAE 2000 mg/Kg body weight p.o.) was administered to one animal after overnight fasting. As the animal survived, four additional animals were dosed sequentially, so that a total of five animals were tested. Animals were observed individually for tremors, convulsions, gait, spasticity, opisthotonus, loss of righting reflex, ataxia, sedation, muscle relaxation, ptosis, lacrimation, diarrhoea, writhes, respiration and changes in skin and fur. Animals were observed individually at 30 minutes interval till first 4 hours after dosing. Then animals were observed after 24 hours and

daily thereafter, for a total of 14 days. No animal died. Therefore, the LD_{50} is greater than 2000 mg/Kg.

On the basis of above result, $1/40^{th}$, $1/20^{th}$ and $1/10^{th}$ part of 2000 mg/Kg dose (ie extract at a dose of 50,100 and 200 mg/Kg body weight p.o.) were chosen for the present study.

Methods

Analgesic activity is studied by 2 methods

- Tail flick method in rat[8]

Rats were divided into following five groups each containing 6 numbers

Group A: Control group-received normal saline (NS) 2 ml/kg p.o.
Group B: Standard group-received tramadol 10 mg/kg p.o.
Group C: Test drug group-received AMSBAE 50 mg/kg p.o.
Group D: Test drug group-received AMSBAE 100 mg/kg p.o.
Group E: Test drug group-received AMSBAE 200 mg/kg p.o.

Tail flick test done by radiant heat method using analgesiometer, was the model used to study central analgesic activity of drug, originally described by D'Amour et al.[8]

In this method, rat was kept in suitable restrainer with tail keeping out of it. Middle part of tail was exposed to source of radiant heat i.e. heated nichrome wire. Small flickering movements were ignored. A Sharp withdrawal of the tail was taken as end point of procedure. Reaction time is, the time interval between placing the tail of rat on source of radiant heat i.e. nichrome wire and sharp withdrawal of tail from it.

In all groups, tail flick test was performed prior to drug administration and at the end of 30, 60, 90 and 120 minutes after drug administration and reaction time was noted. The cut off time of 10 seconds was selected while measuring reaction time, to avoid thermal injury to animals.

From that, percentage of analgesia is calculated by using the formula

$$\%\ \text{Analgesia} = \text{M.P.E} = \frac{\text{T.L.} - \text{B.T.}}{\text{M.L.} - \text{B.L.}} \times 100$$

Where,

M.P.E. - Maximum possible effect
M.L. -Maximum latency or cut off time
T.L. -Test latency or latency at the end of particular period of time
B.L. -Basal latency or control latency

- Acetic acid induced writhes test in mice[9]

Acetic acid induced writhing test was originally described by Koster R et al.[9]

Mice were divided into five groups each containing 6 numbers as mentioned above

NS (2 ml/kg p.o), aspirin (100 mg/kg p.o.) and AMSBAE 50,100 and 200 mg/kg p.o. were administered to control, standard and test groups respectively. Half an hour after the drug treatment, each animal was given 1% acetic acid intra-peritoneally (i.p.) with a volume of 1 ml/100gm body weight to induce the writhes. The mice were individually placed into glass bowl to observe the writhes. First five minutes were allowed to elapse. Then for the next ten minutes observe each animal and numbers of writhes were counted.

From these, the Percentage Inhibition of writhes was calculated by formula

$$\%\ \text{Inhibition of writhes} = \frac{\text{Wc} - \text{Wt.}}{\text{Wc}} \times 100$$

Where,

Wc: number of writhes in control.
Wt : number of writhes in test.

RESULTS

AM significantly increase the mean latency elicited by Tail flick method ($P<0.05$) at 100 and 200 mg/kg as compared to the Normal saline treated rats. Tramadol (10 mg/kg) elicited significant ($P<0.05$) analgesic activity as compared to AMSBAE at the dose of 50 100 and 200 mg/kg treated rats (Table 1).

At 30 minutes, maximum possible effect of AMSBAE (50,100 and 200 mg/kg p.o.) was not significant ($P>0.05$) as compared to tramadol.

AMSBAE shows significant ($P<0.01$) dose dependent analgesic effect. At 120 minutes, all groups showed their maximum effect. While comparing AMSBAE (50 mg/kg p.o.) with AMSBAE (100 and 200 mg/kg p.o.), maximum possible effect of both test groups is more than AMSBAE (50 mg/kg p.o.) and is significant ($P<0.01$) too. Maximum possible effect of AMSBAE (200 mg/kg p.o.) is more and statistically significant when compared with AMSBAE (100 mg/kg p.o.). Maximum possible effect of tramadol is remains high at all the time as compared to all other test groups, and reached to its maximum at 120 minutes (Table 2).

Table 1: Effects of different drugs in tail flick method of analgesia in rats.

Group (n=6), drug and dose	Mean reaction time in seconds (mean±SEM)				
	Basal latency	30 minutes	60 minutes	90 minutes	120 minutes
A - Control (NS 2 ml/kg p.o.)	4.73±0.0212	4.72±0.0240	4.74±0.0240	4.74±0.0230	4.74±0.0256
B - Aspirin (100 mg/kg p.o.)	4.782±0.0307	4.807**±0.0270	5.540**±0.0491	6.383**±0.0454	7.203**±0.0488
C - AMSBAE (50 mg/kg p.o.)	4.885±0.0343	4.903**±0.0358	5.012**$^{\#\#}$±0.0417	5.157**$^{\#\#}$±0.0432	5.207**$^{\#\#}$±0.0414
D - AMSBAE (100 mg/kg p.o.)	4.828±0.0196	4.847**±0.0208	5.083**$^{\#\#}$±0.0328	5.343**$^{\#\#}$±0.0367	5.407**$^{\#\#}$±0.0381
E - AMSBAE (200 mg/kg p.o.)	4.645±0.0503	4.670**$^{\$\$\Re}$±0.0508	5.202**$^{\#\#\$}$±0.0483	5.517**$^{\#\#\$\$}$±0.0691	5.803**$^{\#\#\$\$\Re\Re}$±0.0663

**P<0.01 when compared with control; *P<0.05 when compared with control; ##P<0.01 when compared with Tramadol; #P<0.05 when compared with Tramadol; $$P<0.01 when compared with AMSBAE 50 mg/kg; $P<0.05 when compared with AMSBAE 50 mg/kg; ℜℜP<0.01 when compared with AMSBAE 100mg/Kg; ℜP<0.05 when compared with AMSBAE 100mg/Kg

Table 2: Maximum possible effect of drugs in tail flick method of analgesia in rats.

Group (n=6), drug and dose	Percentage of maximum possible effect (mean±SEM)			
	30 minutes	60 minutes	90 minutes	120 minutes
A - Control (NS 2 ml/kg p.o.)	-	-	-	-
B - Tramadol (10 mg/kg p.o.)	0.479±0.0794	14.53±1.002	30.682±0.8971	46.397±0.9284
C - AMSBAE (50 mg/kg p.o.)	0.352±0.0613	2.483$^{\#\#}$±0.2062	5.318$^{\#\#}$±0.2786	6.295$^{\#\#}$±0.2537
D - AMSBAE (100 mg/kg p.o.)	0.367±0.0328	4.93$^{\#\#}$±0.8466	9.957$^{\#\#\$}$±0.8577	11.195$^{\#\#\$\$}$±0.9308
E - AMSBAE (200 mg/kg p.o.)	0.467±0.0639	10.40$^{\#\$\$\Re\Re}$±0.0990	16.284$^{\#\#\$\$\Re\Re}$±0.6930	21.625$^{\#\#\$\$\Re\Re}$±0.5417

P<0.01 when compared with Aspirin; # P <0.05 when compared with Aspirin; $$ P <0.01 when compared with AMSBAE 50 mg/kg; $ P <0.05 when compared with AMSBAE 50mg/Kg; ℜℜP <0.01 when compared with AMSBAE 100 mg/kg; ℜP <0.05 when compared with AMSBAE 100 mg/kg

Table 3: Effects of different drugs in acetic acid induced writhes method of analgesia in mice.

Group (n=6), drug and dose	Number of writhes (mean±SEM)
A-Control (NS 2 ml/kg p.o.)	34.83±0.4773
B-Aspirin (100 mg/kg p.o.)	7.5**±0.4282
C-AMSBAE (50 mg/kg p.o.)	28.5**$^{\#\#}$±0.3416
D-AMSBAE (100 mg/kg p.o.)	26.33**$^{\#\#\$}$±0.6146
E-AMSBAE (200 mg/kg p.o.)	18.33**$^{\#\#\$\$\Re\Re}$ ± 0.4944

** P <0.01 when compared with control; * P <0.05 when compared with control; ## P <0.01 when compared with Aspirin; # P <0.05 when compared with Aspirin; $$ P <0.01 when compared with AMSBAE 50 mg/kg; $ P<0.05 when compared with AMSBAE 50 mg/kg;ℜℜP <0.01 when compared with AMSBAE 100 mg/kg; ℜP <0.05 when compared with AMSBAE 100 mg/kg

Acetic-acid induced writhes response

Number of writhes in 10 minutes is highest in control group (34.83±0.4773) while least in aspirin group (7.5±0.4282). Number of writhes in all test groups is significant (P<0.01) when compared with control and aspirin group (Table 3).

Table 4: Percentage of inhibition in writhes by drugs in mice.

Group (n=6), drug and dose	Percentage of inhibition	Number of writhes reduced
A-Control (NS 2 ml/kg p.o.)	-	-
B-Aspirin (100 mg/kg p.o.)	78.467±0.9781	27.33
C-AMSBAE (50 mg/kg p.o.)	18.17$^{\#\#}$±0.8228	6.33
D-AMSBAE (100 mg/kg p.o.)	24.40$^{\#\#\$}$±1.080	8.5
E-AMSBAE (200 mg/kg p.o.)	47.37$^{\#\#\$\$\Re\Re}$±0.9852	16.5

A signifiant (P<0.01) inhibition of the writhes is elicited by the AMSBAE at 100 and 200 mg/kg as compared to the NS (Table 3). Standard drug aspirin (100 mg/kg) elicited significant (P<0.01) increase in percentage of inhibition of writhes as compared to NS, AMSBAE (50, 100 and 200 mg/kg) treated mice (Table 4).

DISCUSSION

The tail flick method of analgesia is very effective in evaluating the efficacy and potency of centrally acting analgesic drugs.[8,10]

In the present study radiant heat induced tail flick test is used as a model of algesia which is selective for opioid-like compounds. The effectiveness of analgesic agents in tail flick model is in close resemblance with relief of pain perception in humans.[11] The results obtained in present study indicate that AMSBAE possesses dose-dependent analgesic activity, which is suggestive of central mechanism of action.

Shankarananth V et al using methanolic extract of AM leaves at a dose of 200 and 300 mg/kg body weight p.o. showed significant analgesic activity as compared to diclofenac (10 mg/kg p.o.) in mice.[12] Latency period in diaclofenac group was 8.86 second, while in test group (200 and 300 mg/kg p.o.) it was 6.9 and 7.8 sec. respectively.

Kothari Saroj et al studied with methanol extract of AM leaves (75,150 and 300 mg/kg p.o.) showed significant analgesic activity as compared to control and morphine (1 mg/kg) as a standard in mice.[13] Maximum analgesic effect was seen after 60 minutes in all groups except control. At 60 minutes, latency period in morphine group was 8.33 sec., while in test group (75,150 and 300 mg/Kg p.o.) it was 3.95, 6.06 and 7.65 second respectively.

The results of tail flick method of analgesia in our study indicate that AMSBAE has analgesic activity which was comparable to control and tramadol group.

In the tail flick model, AMSBAE in different doses increase the pain threshold significantly during the period of observation and thus indicates the involvement of a higher centre.

The serotonergic, noradrenergic and opioid neurotransmitter system pathways have been implicated in the inhibitory control of pain in humans and animals.[14] AMSBAE induced analgesic activity may be due to involvement of opioid or monoaminergic pain pathway or both in addition to pain pathways.[13,14]

In the acetic acid induced writhes method, the analgesic action of AMSBAE (50, 100 and 200 mg/kg p.o.) is significant as compared to control and aspirin group. Percentage of analgesia with AMSBAE 50, 100 and 200 mg/kg p.o. is 18.17, 24.40 and 47.37% respectively. In aspirin group, percentage of analgesia is 78.467%. In this method, compounds with percentage analgesia less than 70% are considered to have minimal analgesic activity. 15 Percentage of analgesia in aspirin group is more than 70%.

Percentage of analgesia is less than 70% in all test groups. The writhe induced by acetic acid is a sensitive procedure to assess peripheral mechanism of action of algesics. This response is thought to involve local peritoneal receptors. This test is less time consuming and has been used by many investigators as a simple screening method.

As the acetic acid induced writhing method mainly evaluates peripherally acting analgesics, maximum analgesic activity of aspirin was observed in this method while the analgesic action of AMSBAE was less than that of aspirin but statistically significant.

It is well established that chemical mediators are responsible for the inflammatory pain. The algesic effects of acetic acid are produced due to liberation of mediators such as histamine, serotonin, bradykinin, cytokines and prostaglandins.[16,17]

These factors increase vascular permeability as well as reduce the threshold of nociception and stimulate the terminal of nociceptive fibers.[16] Analgesic activity of AMSBAE may be due to reduction of liberation of these inflammatory mediators.

Kothari Saroj et al studied methanol extract of AM leaves (150 and 300 mg/kg p.o.) showed significant analgesic activity as compared to control and diclofenac as a standard in mice.[13] Percentage of inhibitions of writhes were 28, 58 and 61% in test (150 and 300 mg/kg p.o.) and diclofenac group (5 mg/kg p.o.) respectively.

Arul V et al studied different extracts of the leaves of AM (50 mg/kg i.p.) observed significant protection against acetic acid-induced writhing in mice.[18] Acetone extract showed maximum protection (79.48%), followed by diethyl ether extract (79.38%), chloroform extract (73.36%), petroleum ether extract (72.37%). Results were statistically significant as compared to control and paracetamol 100mg/kg i.p.

Shankarananth V et al studied methanol extract of AM leaves at 100, 200 and 300 mg/kg doses showed significant reduction in writhes as compared to control and diclofenac (10 mg/kg) groups in mice.[12] Number of writhes in diclofenac group are 11.66 followed by 29.33, 16.33 and 13.33 in test groups with 100, 200 and 300 mg/kg doses respectively. Percentages of inhibition were 28.19, 56.57 and 64.55 % in extract received groups at a dose of 100, 200 and 300 mg/kg respectively.

Shankar B et al studied 50 % ethanolic extract of leaves of AM at 100, 200 amd 400 mg/kg doses observed dose dependent reduction in number of writhes. Results were

significant as compared to control and pentazocin 3 mg/kg. Percentage of inhibition was 18.61, 24.45 and 51.58 % in extract treated groups at a dose of 100, 200 and 400 mg/kg respectively.[19] AMSBAE showed significant analgesic activity, thereby establishing its traditional use in painful conditions. However further studies and developments of more purified products of steam bark of AM are required for clinical use.

CONCLUSION

AMSBAE has analgesic activity which is statistically significantly and comparable to Tramadol and Aspirin, in tail flick and acetic acid induced writhing method respectively. Analgesic activity of AMSBAE (200 mg/kg p.o.) is comparable to AMSBAE (100 and 50 mg/kg p.o.) in both methods. LD_{50} of AMSBAE is more than 2000 mg/kg p.o. Thus doses used in study are safe.

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