Journal of Applied Pharmaceutical Science 01 (04); 2011: 121-126

Journal of Applied Pharmaceutical Science

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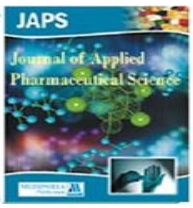

ISSN: 2231-3354
Received: 09-06-2011
Revised : 12-06-2011
Accepted: 14-06-2011

Neuropharmacological study of *Argemone mexicana* Linn.

Sneha Anarthe and Sanjay Chaudhari

Sneha Anarthe
Department of Pharmacognosy, Gokaraju Rangaraju College of Pharmacy, Bachupally, Hyderabad, Andhra Pradesh.

Sanjay Chaudhari
Amrutvahini College of pharmacy, Sangamner, India.

***For Correspondence**:
Mrs. Sneha J. A.
Department of Pharmacognosy, Gokaraju Rangaraju College of Pharmacy,Bachupally, Hyderabad, India, Pin code- 500 090
Email- sneha.pharma@yahoo.co.in,

ABSTRACT

In the present study methanolic and ethyl acetate extracts of *Argemone mexicana* whole plant (Papaveraceae) were tested orally in swiss albino mice at doses of 100 mg/kg, 200 mg/kg and 400 mg/kg b.w. for CNS related activities. Papaveraceae family is known to have CNS depressant activity, so *A. mexicana* was evaluated for CNS activities. Significant central and peripheral nociceptive activity was observed for both extracts. Methanolic and ethyl acetate extract have also showed significant decrease in motor activity and fall off time of animals on rotating rod, along with sedative effect by potentiating phenobarbitone-induced sleeping time. In the acute toxicity study, both extracts was found to be safe upto 2500 mg/kg b.w. These results suggested that methanolic and ethyl acetate extracts of *Argemone mexicana* show analgesic, anxiolytic and sedative effects.

Key words: *Argemone mexicana*, hot plate test, writhing test, locomotor activity, muscle relaxant activity

INTRODUCTION

Argemone mexicana (Papaveraceae) is a prickly glabrous herb with yellow juice and flashy yellow flowers, height of this plant varies between 0.3 to 0.12 m, Leaves are thistle like. Flowering time is all round the year in Indian circumstances and the flowers are scented and hermaphrodite. The plant prefers light sandy soils, requires well-drained soil and can grow in nutritionally poor soil and also prefers acid, neutral and basic (alkaline) soils (Rastogi R. P., 1979). *A. mexicana* is used by traditional healers in Mali to treat malaria (Willcox ML et al., 2007), externally in the treatment of cataracts and internally in the treatment of dropsy and jaundice. The root is used for the treatment of chronic skin diseases and alterative (Chevallier A., 1996, Chopra. R. N. et al 1986). The seeds are used as demulcent, emetic, expectorant, laxative and also used as an antidote in snake poisoning. The seed oil is purgative and used in the treatment of skin problems (Chevallier A., 1996 and Chopra. R. N. et al., 1986). *Argemone maxicana* has been investigated in terms of modern pharmacology for its anti-malarial activity (Merlin L. et al., 2007, Bertrand Graz et al., 2010, M. Sakthivadivel et al., 2003.), Molluscicidal and nematocidal activity (Sushma Singh, 1999, S. Singh 2000), Anticancer activity (Chang, Y.-C, 2003), Anti-bacterial, antifungal and antimicrobial activity (Bhattacharrjee I., 2006, Satish S. 2007, Siddiqui I. A.,2002, A. Osho , 2010.), Hepatoprotective activity (Das P. K. et al., 2009), Antistress and antiallergic activity (Bhalke et al., 2009), Anti-cataleptic activity (Bhalke et al., 2009)., Anti-HIV activity (Chang et al., 2003), Neuropharmcological study (Capasso A. et al., 2002). In the present study *A. mexicana* was evaluated for its analgesic, anxiolytic and sedative activities.

MATERIAL AND METHOD

Plant material and preparation of extracts

The whole *Argemone mexicana* plant was collected in June 2009 from Ahmednagar district, Maharashtra (India). The plant specimen was authenticated from Botanical Survey of India, Pune (Voucher specimen no. YMA1). Plant material was dried under shade and coarsely powdered for extraction. The coarsely powdered whole plant (500g) of *Argemone mexicana* was separately subjected to extraction using ethyl acetate and methanol for 10 days by cold maceration. The methanolic and ethyl acetate extracts were concentrated by rotary vacuum evaporator under reduced pressure and then dried in open air.

Animals

Healthy wistar albino mice of either sex and of approximately the same age, weighing about 30-40 g were used for study. All the mice were housed in polypropylene cages maintained under standard condition (12 h light/12 h dark cycle). All the animals were carefully monitored and maintained in accordance with CPCSEA guidelines on control and supervision of experimental animals. The ethical clearance was obtained from the Institutional Animal Ethics Committee before the experiment.

ANALGESIC ACTIVITY

Hot plate test

Central analgesic activity for *A. mexicana* whole plant was evaluated using hot plate method as per described by Woolfe and MacDonald. Albino male mice were divided into eight groups containing six animals each.

Group-I- control (received only vehicle)
Group-II -standard drug pentazocine (50 mg/kg, i.p.)
Group-III- 100 mg/kg b.w. methanolic extract
Group IV-200 mg/kg b.w. methanolic extract
Group V- 400 mg/kg b.w. methanolic extract
Group VI-100 mg/kg b.w. ethyl acetate extract
Group VII- 200 mg/kg b.w. ethyl acetate extract
Group VIII- 400 mg/kg b.w. ethyl acetate extract

Individual mice was placed on the hot plate which was maintained at 55 ^{0}C ± 1 ^{0}C, and latency of nociceptive response such as jumping, flicking of a hind limb and licking was noted. And after administration of extracts, the readings were recorded at 0, 30, 60, 90, 120, 150 and 180 minutes time interval. The experiment was terminated by 20 second after their placement on the hot plate to avoid damage to the paws of animals.

Writhing test

Peripheral analgesic activity for *A. mexicana* was evaluated using writhing test (Koster R et al., 1959). Albino male mice (30-40 g) were grouped into eight groups of six animals each.

Group-I- control (received only vehicle)
Group-II -standard drug paracetamol (50 mg/kg, i.p.)
Group-III- 100 mg/kg b.w. methanolic extract
Group IV-200 mg/kg b.w. methanolic extract
Group V- 400 mg/kg b.w. methanolic extract
Group VI-100 mg/kg b.w. ethyl acetate extract
Group VII- 200 mg/kg b.w. ethyl acetate extract
Group VIII- 400 mg/kg b.w. ethyl acetate extract

Before administration of acetic acid, extracts and standard drug, each mice was placed in the glass beakers. 0.1 ml of 0.6 % of acetic acid solution was injected intraperitoneally to each animal. Then the animals were allowed to elapse for 5 minutes, after administration of acetic acid and number of writhes was recorded individually to each animal for the period of 30 minutes.

Locomotor activity

The healthy adult albino mice (30-40 g) were firstly divided into eight groups containing six animals each.

Group-I- control (received only vehicle)
Group-II -standard drug diazepam (4 mg/kg i.p.)
Group-III- 100 mg/kg b.w. methanolic extract
Group-IV-200 mg/kg b.w. methanolic extract
Group-V- 400 mg/kg b.w. methanolic extract
Group-VI-100 mg/kg b.w. ethyl acetate extract
Group-VII- 200 mg/kg b.w. ethyl acetate extract
Group-VIII- 400 mg/kg b.w. ethyl acetate extract

After thirty minutes of standard drug and extract administration, each animal was placed in photoactometer individually and then the locomotor activity was counted for 10 minutes (Dewan S, 2000, Amos s, 2001).

Motor coordination (Muscle relaxant activity)

For the assessment of the motor co-ordination test, albino mice (30-40 g) were divided into eight groups containing six animals each group.

Group-I- control (received only vehicle)
Group-II -standard drug diazepam (2 mg/kg, i.p.)
Group-III- 100 mg/kg b.w. methanolic extract
Group-IV-200 mg/kg b.w. methanolic extract
Group-V- 400 mg/kg b.w. methanolic extract
Group-VI-100 mg/kg b.w. ethyl acetate extract
Group-VII- 200 mg/kg b.w. ethyl acetate extract
Group-VIII- 400 mg/kg b.w. ethyl acetate extract

Rota-rod device was used for the assessment of the experiment. The mice were positioned on rota-rod which was set at a rate of 16 revolutions per minutes. The fall off time for each animal was noted. The difference in the fall off time from the rotating rod was noted at the interval of 30 minutes for 3h (Ozturk et al., 1996; Perez et al., 1998).

Effect on Phenobarbitone sodium sleep

For the evaluation of phenobarbitone sodium induced sleeping test, albino mice (30-40 g) were divided into eight groups containing six animals each group.

Table no. 1 Analgesic activity of methanolic and ethyl acetate extracts of *A. mexicana* by Eddy's hot plate method:

Group	Treatment	Mean reaction time in minutes (min ±SEM)					
		0min	30min	60min	120min	150min	180min
I	Control (Normal saline)	5.29± 0.0288	5.3± 0.0208	4.96± 0.0409	5.09± 0.1217	5.35± 0.1590	5.48± 0.1350
II	Pentazocin (50 mg/kg)	5.42± 0.0321	9.45± 0.1198	13.96± 0.0288	21.29± 0.0466	19.42± 0.0556	16.01± 0.0176
III	ME-100mg/kg	5.04± 0.0240	6.21± 0.0832*[a]	8.22± 0.0721*[a]	11.06± 0.0176*[a]	10.42± 0.0829*[a]	9.44± 0.0240*[a]
IV	ME-200mg/kg	4.91± 0.0371	7.30± 0.1167*[a]	9.36± 0.0480*[a]	13.29± 0.0864*[a]	12.34± 0.0819*[a]	10.31± 0.0887*[a]
V	ME- 400mg/kg	5.2± 0.0208	7.76± 0.1490*[a]	10.34± 0.0744*[a]	15.44± 0.1365*[a]	13.46± 0.0866*[a]	11.57± 0.0929*[a]
VI	EA-100mg/kg	4.55± 0.1286	5.94± 0.0230*[a]	7.35± 0.0768*[a]	10.55± 0.1322*[a]	9.08± 0.0296*[a]	8.25± 0.0584*[a]
VII	EA-200mg/kg	4.91± 0.0115	6.24± 0.0693*[a]	8.44± 0.0763*[a]	12.43± 0.0448*[a]	10.17± 0.1200*[a]	9.48± 0.1110*[a]
VIII	EA-400mg/kg	5.07± 0.0176	7.31± 0.1185*[a]	9.61± 0.1015*[a]	13.42± 0.0731*[a]	11.32± 0.0545*[a]	9.08± 0.0384*[a]

Results are expressed as ± SEM (n=6). Data processed by one way ANOVA followed by Dunnett's test, * $p<0.01$ significant when compared to control group. [a]$p<0.01$ significant when compared to standard group.

Group-I- control (received only vehicle)
Group-II -standard drug diazepam (1 mg/kg, i.p.)
Group-III- 100 mg/kg b.w. methanolic extract
Group-IV-200 mg/kg b.w. methanolic extract
Group-V- 400 mg/kg b.w. methanolic extract
Group-VI-100 mg/kg b.w. ethyl acetate extract
Group-VII- 200 mg/kg b.w. ethyl acetate extract
Group-VIII- 400 mg/kg b.w. ethyl acetate extract

Phenobarbitone sodium (40 mg/kg b.w.) was administered to individual animal later than 30 minutes of extract and standard drug administration. And all the animals were observed for onset of sleep and extent of sleep with condition being loss of righting reflex (Wambebe, 1985; Rolland et al., 1991).

Statistical analysis

Statistical analysis was performed using Graph Pad prism 3. All the results were expressed as mean ± standard error of mean (S.E.M.) and analyzed for ANOVA and post hoc Dunnet's *t*-test (Multiple). Differences between groups were considered significant at $p<0.05$, $p<0.01$ levels.

RESULT AND DISCUSSION

Acute toxicity studies for methanolic and ethyl acetate extract of *A. mexicana* showed no mortality till doses of 2.5 g/kg b.w. even after 72 h. All mice were compared to normal animals for their awareness, vocalization, tremors, righting reflex, pain, salivation and lacrimation.

In present study methanolic and ethyl acetate extract of *A. mexicana* whole plant was studied for CNS depressant activity at doses of 100 mg/kg, 200 mg/kg and 400 mg/kg b.w. with various animal models such as analgesic activity by hot plate method and acetic acid induced writhing test, locomotor activity, motor coordination (muscle relaxant activity) and phenobarbitone induced sleeping time.

In the assessment of analgesic activity, methanolic extract and ethyl acetate extracts of *A. mexicana* showed significant central analgesic activity (Table 1) at dose of 200 mg/kg as compare to control ($p<0.01$) and standard pentazocine ($p<0.01$). For peripheral analgesic activity percentage inhibition for ethyl acetate extract and methanol extract at dose 200 mg/kg b.w. was found to be 53.34 % and 52.84 %. And ethyl acetate extract was found to be more potent as compare to methanol extract. But both extracts showed significant peripheral activity when results were compared to control ($p<0.01$) and standard paracetamol ($p<0.01$). As methanolic and ethyl acetate extracts of *A. mexicana* also showed remarkably locomotor activity on photoactometer (Table 3), amongs both extracts methanolic extract showed significant reduction in motor activity at doses of 200 mg/kg, when results are compared to control ($p<0.01$) and standard diazepam ($p<0.01$).

Table no. 2 Analgesic activity of methanolic and ethyl acetate extracts of *A. mexicana* by acetic acid induced method

Group	Treatment	Number of writhing	Percent inhibition
I	Control (Normal saline)	67.80± 0.1590	-
II	Paracetamol (50 mg/kg)	20.04 ± 0.0763	70.44
III	ME-100mg/kg	43.14 ± 0.0550*[a]	36.37
IV	ME-200mg/kg	31.97 ± 0.0437*[a]	52.84
V	ME- 400mg/kg	30.10 ± 0.0176*[a]	55.60
VI	EA-100mg/kg	41.31 ± 0.0569*[a]	39.07
VII	EA-200mg/kg	31.63 ± 0.1212*[a]	53.34
VIII	EA-400mg/kg	29.27 ± 0.0841*[a]	56.82

Results are expressed as ± SEM (n=6). Data processed by one way ANOVA followed by Dunnett's test, * $p<0.01$ significant when compared to standard group. [a]$p<0.01$ significant when compared to control group.

In the assessment of muscle relaxant test, methanolic and ethyl acetate extracts of *A. mexicana* showed significant reduction in fall off time of animals (sec) on rota rod (Table no. 4) when

results were compared to control group ($p<0.01$) and standard diazepam ($p<0.01$) and in case of phenobarbitone induced sleeping test, methanolic extract at dose of 200 mg/kg b.w. significantly potentiate phenobarbitone induced sleeping time (Table 5) as compared to control ($p<0.01$) and standard ($p<0.01$).

Table no. 3 Effect of methanolic and ethyl acetate extracts of *A. mexicana* on locomotor activity

Group	Treatment	Locomotor activity observed for 10 min	
		Before dosing	After dosing
I	Control (Normal saline)	178.10± 0.0726	178.37± 0.3327
II	Diazepam (4 mg/kg)	177.54 ± 0.1374	83.97± 0.1332
III	ME-100mg/kg	178.24± 0.1593	128.43± 0.0266*
IV	ME-200mg/kg	177.65± 0.1202	110.32 ± 0.0523*[a]
V	ME- 400mg/kg	177.76± 0.0700	108.46 ± 0.0796*[a]
VI	EA-100mg/kg	177.65± 0.0491	132.39 ± 0.1313*
VII	EA-200mg/kg	178.3 ± 0.06506	113.50 ± 0.0617*[a]
VIII	EA-400mg/kg	178.54± 0.1378	110.45 ± 0.2245*[a]

Results are expressed as ± SEM (n=6). Data processed by one way ANOVA followed by Dunnett's test, * $p<0.01$ significant when compare control group. [a]$p<0.01$ significant when compared to standard group.

As remarkable analgesic activity of methanolic extract at dose 200 mg/kg b.w. was seen in Eddy's hot plate method and acetic acid induced writhings. The hot plate test is widely used for assessment of central antinociceptive activities, having tendency to respond to the pain stimuli through neuronal pathways (Chapman et al., 1985; Morales et al., 2001). In general, acetic acid writhing test is used for evaluation of peripheral antinociceptive activities, as writhing test is useful to differentiate between central and peripheral nociception (Le Bars et al., 2001) and acetic acid injection induces peritoneal inflammation, which may triggers a response characterized by writhing (Koster et al., 1959).

This study demonstrated that acetic acid indirectly induces endogenous release of pain mediators (such as prostaglandins, kinins, histamin, etc.) that stimulate the nociceptive neurons, which are responsive to non- steroidal anti-inflammatory drugs and opioids (Derardt et al., 1980; Sánchez-Mateo et al., 2006; Sulaiman et al., 2008).

The locomotor activity was also assessed for methanolic and ethyl acetate extract by actophotometer but methanolic extract was found to be more potent. As it showed decrease in locomotion and grip strength on rota rod was also decreased (Leewanich et al., 1996) which reveals the CNS depressant activity. The CNS depression may be due to the increase in the GABA concentration in brain (Nagarjun et al., 2003). The pentobarbitone-induced sleep test, also significantly showed sedative effect for methanolic and ethyl acetate extracts but methanolic extract was found to be potent.

As preliminary Phytochemical investigation showed the presence of phenolics, flavonoids, steroids, alkaloids and tannins, which may be responsible for the CNS depressant activity. The above studies indicate that the methanolic extract of *A. mexicana* whole plant possesses analgesic, sedative, and anxiolytic activity.

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Table no. 4 Effect of methanolic and ethyl acetate extracts of *A. mexicana* on muscle relaxant activity.

Group	Treatment	Fall of time in seconds (sec ±SEM)					
		0min	30min	60min	120min	150min	180min
I	Control (Normal saline)	35.52± 0.0470	35.71± 0.1595	35.76± 0.2084	35.4± 0.1595	35.51± 0.0560	35.72± 0.1757
II	Diazepam (2 mg/kg)	36.17± 0.0578	28.21± 0.0993	19.15± 0.0458	14.06± 0.0264	20.16± 0.0260	25.25± 0.1115
III	ME-100mg/kg	35.56± 0.1081	33.14± 0.0352*[a]	31.35± 0.1058*[a]	28± 0.0592*[a]	29.33± 0.0393*[a]	27.42± 0.0602*[a]
IV	ME-200mg/kg	35.71± 0.0832	32.13± 0.0688*[a]	27.32± 0.0635*[a]	23.25± 0.0416*[a]	25.45± 0.1868*[a]	26.80± 0.1073*[a]
V	ME- 400mg/kg	35.99± 0.0554	31.29± 0.0617*[a]	25.58± 0.1418*[a]	21.35± 0.0433*[a]	23.58± 0.2098*[a]	26.24± 0.0819*[a]
VI	EA-100mg/kg	36.36± 0.0480	33.98± 0.0173*[a]	32.13± 0.0208*[a]	29.38± 0.0360*	30.31± 0.0845*[a]	31.35± 0.0674*
VII	EA-200mg/kg	35.31± 0.0536	33.03± 0.0321*[a]	28.33± 0.1475*[a]	24.46± 0.0786*[a]	25.08± 0.0556*[a]	27.31± 0.2488*[a]
VIII	EA-400mg/kg	35.18± 0.1012	32.08± 0.0425*[a]	27.32± 0.1281*[a]	23.02± 0.0409*[a]	24.15±s 0.0328*[a]	27.32± 0.2136*[a]

Results are expressed as ± SEM (n=6). Data processed by one way ANOVA followed by Dunnett's test, * $p<0.01$ significant when compared to standard group. [a]$p<0.01$ significant when compared to control group.

Table no. 5 Effect of methanolic and ethyl acetate extracts of *A. mexicana* on phenobarbitone induced sleeping time.

Group	Treatment	Mean sleeping time in min.
I	Control (Normal saline)	23.36± 0.05000
II	Phenobarbitone (40 mg/kg)	74.53 ± 0.2661
III	ME-100mg/kg	35.22 ± 0.08988*
IV	ME-200mg/kg	43.41 ± 0.1368*[a]
V	ME- 400mg/kg	48.58 ± 0.0696*[a]
VI	EA-100mg/kg	37.25 ± 0.1146*
VII	EA-200mg/kg	45.46 ± 0.1375*[a]
VIII	EA-400mg/kg	47.33 ± 0.0783*[a]

Results are expressed as ± SEM (n=6). Data processed by one way ANOVA followed by Dunnett's test, * $p<0.01$ significant when compared to control group. [a]$p<0.01$ significant when compared to standard group.

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