Original Research Article

Anti-nociceptive activity of Aloe vera gel extract in graded doses by using Hot water bath in Albino rats

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Abstract

Background: Pain has been described by the International Association for the Study of Pain as an "unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage". **Objective:** To evaluate anti-nociceptive activity of Aloe vera gel extract in graded doses by using Hot water bath in Albino rats. **Materials and methods:** The present study was conducted in the Department of Pharmacology, Kamineni Institute of Medical Sciences (KIMS) from October 2012 - September 2014. It is undertaken to evaluate the anti-nociceptive effect of Aloe vera in animal models of pain in Albino rats. **Results:**Aloe vera in the doses of 200mg/kg and 400mg/kg orally produced significant anti-nociceptive effect in comparison to control group (DW).The standard drug tramadol in the dose of 20mg/kg orally also produced significant anti-nociceptive effect in comparison to control group (DW). Maximum possible effect in percentage (MPE%) was calculated at 120 min with Aloe vera 400mg/kg and Tramadol 20mg/kg and it was observed that Tramadol 20mg/kg produced more MPE% (90.63 ± 2.32; 77.93 ±2.35; 33.94 ± 1.29 respectively) in comparison to Aloe vera 400mg/kg (80.16 ± 2.27; 46.86 ± 1.75; 21.97 ± 1.01 respectively) indicating Tramadol is more potent than Aloe vera. **Conclusion:L** Aloe vera leaf gel extract powder (dissolved in distilled water) possesses anti-nociceptive activity at 200 mg/kg and 400 mg/kg dosage at 60, 90 and 120 minutes when given orally in in albino rats.

Keywords: anti-nociceptive activity, Hot water bath, Aloe vera gel extract, Albino rats

Introduction

Pain is a reaction of the body to harmful stimuli and is therefore a protective early warning system, the sensation of pain in postoperative patients, cancer patients, and other chronic pain patients has little positive effect.

Nociception is the process of detection, transduction and transmission of noxious stimuli. Stimuli generated from the thermal, mechanical or chemical tissue damage may activate nociceptors, which are free nerve endings. Each sensory unit includes an end-organ receptor, accompanying axon, dorsal root ganglion and axon terminals in the spinal cord. [1]

The nature of pain is highly subjective. Pain has both sensory (somatic) and psychological (affective) components. One person may feel pain in response to noxious stimuli, while another person may disregard the stimuli. The affective (psychological) aspects of pain play a critical role in pain perception.

The principal objective of alleviating pain is to remove or abolish the cause of pain. But it is not always possible to do so. Hence, analgesics are used for the symptomatic treatment of pain. The analgesics are of two types: Opioids and Non-Opioids.

Non-steroidal anti-inflammatory drugs (NSAIDs) are a group of chemically dissimilar agents that differ in their antipyretic, analgesic, and anti-inflammatory activities. They act primarily by inhibiting the cyclooxygenase enzymes that catalyze the first step in prostanoid biosynthesis. [2]This leads to decreased prostaglandin synthesis with both beneficial and unwanted effects like cardiac toxicities, peptic ulceration, and perforation of stomach, blood dyscrasias and renal toxicities.

Aloe vera is widely found in subtropical and tropical areas of the world. Among all 400 species of Aloe, Aloe barbadensisMiller [syn. Aloe vera(L.)] is considered to be the most biologically active plant. [3]Besides acting as a therapeutic agent, it has long been used in dietary supplements and for cosmetic purposes. [4]

The healing of burn wounds is one of the main indications for Aloe veragel use in both animal and human clinical Studies. [5] Recently, it has been shown that Aloe veracan facilitate wound healing in post haemorroidectomy patients. [6]Aloe vera decreased chronic anal fissure pain. [7]

Only a few studies were conducted to know the analgesic effect. So the present study has been planned to evaluate anti-nociceptive activity of Aloe vera gel extract in graded doses by using hot water bath in Albino rats.

Materials & Methods

The present randomized controlled study was conducted in the Department of Pharmacology, Kamineni Institute of Medical Sciences (KIMS) from October 2012 - September 2014. It was undertaken to evaluate the anti-nociceptive effect of Aloe vera in animal models of pain in Albino rats. It was conducted with prior permission of Institutional Animal Ethics Committee.

Albino rats (150-200 gm) of both sexes procured from National Institute of Nutrition, Hyderabad were used. The animals housed in central animal house, KIMS under standard laboratory conditions, maintained on 12:12 light-dark cycle and had free access to food and water.

Models for Pain

1. Pain induced by direct heat of Thermal type by Hot Water Bath method in Albino rats.

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The animals were acclimatized to laboratory conditions fifteen days before the tests. Each animal was used only once in the experiment.

Drugs and Chemicals: Aloe vera leaf gel dried powder: Bhaskara Biotech.
Tramadol: Zydus Cadila.
Distilled water.

Drug Administration: All drugs were administered orally using oral feeding tube. For control rats, distilled water was given orally. The standard drug Tramadol (10 mg/kg, 20 mg/kg) was dissolved in distilled water and given orally to standard group rats. Aloe vera leaf gel dried powder (100 mg/kg, 200 mg/kg and 400 mg/kg) was dissolved in distilled water and given orally to test group rats.

Tail Immersion Test [8]**:**

Instruments And Apparatus For Tail Immersion Test:
Hot Water Bath with thermostat control.

Principle: Conduction heat (direct heat) is applied to the distal 5 cm of the tail by immersing it into the hot water (55±0.5°C) directly.

Description of apparatus: It is a double walled instrument with Thermostat Electric concentric rings. Chamber measuring 16" x 15" x 4" is used for measuring tail withdrawal latency i.e. the time duration from immersion of tail in hot water (55±0.5°C) to withdrawal of tail from hot water.

Tail immersion test by hot water-bath: Albino rats of either sex were selected by the process of randomization and rats which showed reaction time of less than 6 sec were used for experimental purpose. Rats were weighed and divided into 7 groups containing 6 animals in each group. The tail withdrawal latency was measured at basal level i.e. at 0 minute, i.e. immediately after giving the drug, and then successively at 30 min, 60 min, 90 min, 120 min of duration after drug administration. Tail withdrawal latency is the time duration from immersing the tail in hot water bath, which is maintained at 55±0.5°C temperature by using thermostat control, till the withdrawal of the tail from hot water bath. Distilled water treatment used as control. The anti-nociceptive activity was considered as positive when reaction time is more than 6 sec and within 15 seconds. Cut-off time was taken as 15 sec in order to prevent the damage to the rat tail.

Fig 1: **Hot Water Bath**

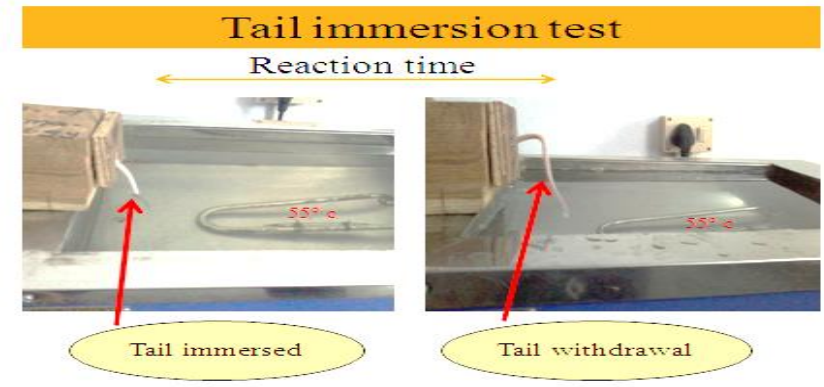

Fig 2: Tail immersion test procedure

Statistical analysis: ANOVA test was used for calculation for statistical significance in between groups. p value < 0.05 is considered as statistically significant.

Maximum possible effect in percentage (MPE %) at 120 minutes is calculated in each group for calculating statistical significance.

$$\text{MPE\%} = \frac{\text{(Post Drug Latency – Pre Drug Latency)}}{\text{(Cut-Off Time – Pre Drug Latency)}} \times 100$$

Results

Tail withdrawal latency (sec) after tail immersion in warm water (55 ± 0.5^0 C) was recorded at 0 min, 30 min, 60 min, 90 min and 120 min after drug administration. Oral administration (p.o) of Aloe vera increased the tail withdrawal latency period (sec) (Mean ± SE) in the doses of 200 mg/kg and 400 mg/kg at 60 min (6.08±0.15, 7.17±0.10 respectively), 90 min (6.75±0.21, 8.00±0.18 respectively) and 120 min (7.50±0.18, 8.58±0.20 respectively) interval in-comparison to control (DW) treatment group (2.92±0.15, 3.08±0.15, 3.17±0.17 respectively) (Table no. 3, 4, 5), indicating Aloe vera can produce

anti-nociceptive effect in tail immersion test. However, there is no much increase in the tail withdrawal latency in the Aloe vera 100 mg/kg (p.o) treatment at 60, 90 and 120 min (3.08±0.15, 3.00±0.13, 3.50±0.18 respectively) in comparison to control (DW) treatment group (Table no. 2, 5).

Oral (p.o) administration of known analgesic drug Tramadol in the anti-nociceptive dose of 20 mg/kg produced increase in the tail withdrawal latency 60, 90 min, 120 min (8.83±0.21, 10.58±0.24, 12.25±0.31, respectively) in comparison to control (DW) treatment group (2.92±0.15, 3.08±0.15, 3.17±0.17 respectively) (Table no. 1,5). However there is no much increase in the tail withdrawal latency in the Tramadol 10 mg/kg (p.o) treatment at 60, 90 min, 120 min (2.92±0.15, 2.92±0.83, 3.08±0.15 respectively) in comparison to control (DW) treatment group (Table no. 5).Combination treatment of low doses of both Aloe vera 100 mg/kg + Tramadol 10 mg/kg did not increase the tail withdrawal latency at 60, 90 and 120 min (3.17±0.10, 3.33±0.10, 3.42±0.15 respectively) in-comparison to control (DW) treatment group or Aloe vera 100 mg/kg (3.08±0.15, 3.00±0.13, 3.50±0.18 respectively) alone, or Tramadol 10 mg/kg (2.92±0.15, 2.92±0.83, 3.08±0.15 respectively) alone (Table no. 2, 5).Maximal possible effect (MPE) in tail withdrawal latency in percentage (%) at 120 min was calculated in Aloe vera 200 mg/kg, Aloe vera 400 mg/kg and Tramadol 20 mg/kg (38.38±0.93, 46.86±1.75, 77.93±2.35 respectively) which is more and statistically significant in comparison to control group (4.03 ±1.03) (Table no. 20, 33, 34, 35). These results suggest that Aloe vera 200 mg/kg, Aloe vera 400 mg/kg and Tramadol 20 mg/kg can produce significant anti-nociceptive effect in the tail immersion test model in Albino rats. However, intergroup comparison of MPE (%) shown that Aloe vera 400 mg/kg (46.86±1.75) is not comparable with Tramadol 20 mg/kg (77.93±2.35) (Table no. 20, 33, 34, 35). MPE (%) in combination group Aloe vera 100 mg/kg + Tramadol 10 mg/kg (5.38 ±1.70) is not significant compared with Aloe vera 100 mg/kg (5.50±0.89) alone or Tramadol 10 mg/kg (3.92±2.01) alone indicating Aloe vera cannot potentiate anti-nociceptive effect of Tramadol

Table 1: Tail Withdrawal Latency in seconds of Tramadol 20 mg/kg (Analgesic dose) (p.o)

Sl No	Tail Withdrawal Latency in seconds				
	0 min	30 min	60 min	90 min	120 min
1	2.50	2.50	8.50	10.00	12.00
2	2.50	3.00	9.00	10.00	12.50
3	2.00	2.50	8.00	10.50	12.00
4	3.00	3.00	9.50	11.00	13.00
5	3.00	3.50	9.00	11.50	13.00
6	2.50	3.00	9.00	10.50	11.00
Total	15.50	17.5	53.00	63.50	73.50
Mean	2.58	2.92	8.83	10.58	12.25
SD	0.38	0.38	0.52	0.58	0.76
SE	0.15	0.15	0.21	0.24	0.31

Table 2: Tail Withdrawal Latency in seconds of Aloe vera 100 mg/kg (p.o.)

Sl No	Tail Withdrawal Latency in seconds				
	0 min	30 min	60 min	90 min	120 min
1	2.50	3.00	3.00	2.50	3.00
2	3.00	2.50	3.00	3.00	4.00
3	2.50	3.00	2.50	3.00	3.00
4	3.00	3.50	3.50	3.00	3.50
5	3.00	3.00	3.50	3.00	3.50
6	3.00	3.50	3.00	3.50	4.00
Total	17.00	18.50	18.50	18.00	21.00
Mean	2.83	3.08	3.08	3.00	3.50
SD	0.26	0.38	0.38	0.32	0.45
SE	0.11	0.15	0.15	0.13	0.18

Table 3: Tail Withdrawal Latency in seconds of Aloe vera 200 mg/kg (p.o.)

Sl No	Tail Withdrawal Latency in seconds				
	0 min	30 min	60 min	90 min	120 min
1	2.50	3.00	5.50	6.00	7.00
2	3.00	3.50	6.00	6.50	7.50
3	2.50	3.00	6.00	7.00	7.50
4	3.50	3.50	6.50	7.50	8.00
5	3.00	3.00	6.50	7.00	8.00
6	2.50	3.00	6.00	6.50	7.00
Total	17.00	19.00	36.50	40.50	45.00
Mean	2.83	3.17	6.08	6.75	7.50
SD	0.41	0.26	0.38	0.52	0.45
SE	0.17	0.11	0.15	0.21	0.18

Table 4: Tail Withdrawal in seconds of Aloe vera 400 mg/kg (p.o.)

Sl No	Tail Withdrawal Latency in seconds				
	0 min	30 min	60 min	90 min	120 min
1	3.00	3.00	7.00	7.50	8.00
2	2.50	3.00	7.50	8.50	9.00
3	3.00	3.50	7.00	7.50	8.00
4	2.50	3.00	7.00	8.00	8.50
5	3.50	3.50	7.50	8.00	9.00
6	3.00	3.50	7.00	8.50	9.00
Total	17.50	19.50	43.00	48.00	51.50
Mean	2.92	3.25	7.17	8.00	8.58
SD	0.38	0.27	0.26	0.45	0.49
SE	0.15	0.11	0.10	0.18	0.20

Table 5: Comparison of tail withdrawal latency (in sec) of Aloe vera with different groups (Mean ± SE)

	0 min	30 min	60 min	90 min	120 min
Control (DW)	2.67±0.17	3.00±0.18	2.92±0.15	3.08±0.015	3.17±0.17
Tramadol (10 mg/kg)	2.58±0.15	2.92±0.15	2.92±0.15	2.92±0.83	3.08±0.15
Tramadol (20 mg/kg)	2.58±0.15	2.92±0.15	8.83±0.21	10.58±0.24	12.25±0.31
Aloe vera (100 mg/kg)	2.83±0.11	3.08±0.15	3.08±0.15	3.00±0.13	3.50±0.18
Aloe vera (200 mg/kg)	2.83±0.17	3.17±0.11	6.08±0.15	6.75±0.21	7.50±0.18
Aloe vera (400 mg/kg)	2.92±0.15	3.25±0.11	7.17±0.10	8.00±0.18	8.58±0.20
Aloe vera 100 mg/kg + Tramadol 10 mg/kg	2.75±0.11	2.92±0.15	3.17±0.10	3.33±0.10	3.42±0.15

Aloe vera 200 mg/kg and 400 mg/kg (p.o.) produced dose dependent increase in tail withdrawal latency (sec) at 60 min, 90 min and 120 min in comparison to Distilled water (control) 0.5 ml p.o.

Tramadol 20 mg /kg p.o. produced increase in tail withdrawal latency (sec) at 60 min, 90 min, and 120 min in comparison to Distilled water (control) 0.5 ml p.o.

Combination group Aloe vera 100 mg/kg + Tramadol 10 mg /kg did not produce much increase in tail withdrawal latency (sec) at 60 min, 90 min and 120 min in comparison to Distilled water (control) 0.5 ml (p.o), Aloe vera 100 mg/kg alone and Tramadol 10 mg /kg alone.

Table 6: MPE (%) Of Tail Withdrawal Latency In Various Drug Pre- Treatment Groups

Sl No	CTRL	T 10	T 20	AV 100	AV 200	AV 400	AV100 + T 10
1	3.85	0.00	76.00	4.00	36.00	41.67	8.00
2	4.00	0.00	80.00	8.33	37.50	52.00	0.00
3	4.17	4.00	76.92	4.00	40.00	41.67	0.00
4	0.00	8.00	83.33	4.17	39.13	48.00	8.00
5	8.00	11.54	83.33	4.17	41.67	47.83	8.33
6	4.17	0.00	68.00	8.33	36.00	50.00	8.00
Total	24.19	23.54	467.58	33.00	230.30	281.17	32.33
Mean	4.03	3.92	77.93	5.50	38.38	46.86	5.38
SD	2.53	4.91	5.76	2.19	2.28	4.30	4.17
SE	1.03	2.01	2.35	0.89	0.93	1.75	1.70

CTRL – Control, T 10 – Tramadol 10 mg/kg, T 20 – Tramadol 20 mg/kg, AV 100 – Aloe vera 100mg/kg, AV 200 – Aloe vera 200mg/kg, AV 400 – Aloe vera 400mg/kg, AV 100 + T 10 – Aloe vera 100 mg/kg + Tramadol 10 mg/kg

MPE in % is increased in Tramadol 20 mg/kg, Aloe vera 200 mg/kg and Aloe vera 400 mg/kg in comparison to control group. Further comparison showed there is no much increase in MPE in % of tail withdrawal latency of combination group of Aloe vera 100 mg/kg + Tramadol 10 mg/kg in comparison to Aloe vera 100 mg/kg alone and Tramadol 10mg/kg alone.

Discussion

Tail withdrawal latency (sec) after tail immersion in warm water (55 ± 0.5^0 C) was recorded at 0 min, 30 min, 60 min, 90 min and 120 min after drug administration.Oral administration(p.o) of Aloe vera increased the tail withdrawal latency period (sec) (Mean ± SE) in the doses of 200 mg/kg and 400 mg/kg at 60 min (6.08±0.15, 7.17±0.10 respectively), 90 min (6.75±0.21, 8.00±0.18 respectively) and 120 min (7.50±0.18, 8.58±0.20 respectively) interval in comparison to control (DW) treatment group (2.92±0.15, 3.08±0.15, 3.17±0.17 respectively) (Table 3,4,5), indicating Aloe vera can produce anti-nociceptive effect in tail immersion test.Oral (p.o) administration of known analgesic drug Tramadol in the anti-nociceptive dose of 20 mg/kg produced increase in the tail withdrawal latency 60, 90 min, 120 min (8.83±0.21, 10.58±0.24, 12.25±0.31, respectively) in comparison to control (DW) treatment group (2.92±0.15, 3.08±0.15, 3.17±0.17 respectively) (Table no. 1,5) indicating anti-nociceptive activity of Tramadol in dose of 20mg/kg p.o. Further Maximum possible (MPE) effect of Tramadol 20 mg/kg (77.93± 2.35) is significantly more than MPE effect of Aloe vera 400 mg/kg (46.86 ± 1.75) suggesting that Tramadol is more potent anti-nociceptive than Aloe vera in tail immersion model also. MPE (%) of combination group (low doses) Aloe vera 100 mg/kg+ Tramadol 10 mg/kg (5.38±1.70) did not show any significant change with Aloe vera 100 mg/kg (5.50±0.89) alone or Tramadol 10 mg/ kg (3.92±2.01) alone indicating Aloe vera cannot potentiate anti-nociceptive effect of Tramadol(Table 6) in tail immersion model also. Thirunethira-nkarpagam et al 2011[9] also studied the effect of Aloe vera in the doses of 100 mg/kg, 200mg/kg and 400mg/kg intra peritoneal route in tail immersion model in albino rats. Aloe vera in the doses of 200mg/kg and 400mg/kg produced significant increase in the tail withdrawal latency in the present study and Thirunethirankarpagam et al study suggesting the results of present study are comparable with the study of Thirunethirankarpagam et al.

However, Thirunethirankarapagam et al observed increase in the tail withdrawal latency even with Aloe vera 100mg/kg also in comparison to the present study results. The difference might be due

to intra peritoneal administration in Thirunethirankarapagam et al study whereas oral administration in the present study.

Conclusion

Aloe vera leaf gel extract powder (dissolved in distilled water) possesses anti-nociceptive activity at 200 mg/kg and 400 mg/kg dosage at 60, 90 and 120 minutes when given orally in albino rats.

Anti-nociceptive effect of Tramadol 20 mg/kg in terms of maximum possible effect in percentage (MPE%) at 120 minutes is significantly more than Aloe vera 400 mg/kg orally suggesting Tramadol is more potent anti-nociceptive than Aloe vera in tail immersion.Combination of sub-antinociceptive doses of Aloe vera 100 mg/kg and Tramadol 10mg/kg did not show significant anti-nociceptive activity at 60, 90 and 120 minutes suggesting that Aloe vera had no synergistic action with Tramadol.

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