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Research Article

AN EXPERIMENTAL STUDY ON THE ANALGESIC ACTION OF *PADMAK AGAD*

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ABSTRACT

Padmak Agad is indicated in all types of *Luta and Keet Visha.* According to *Acharya Vagbhatta*, heaviness in head and eyes, coma, dizziness, dyspnoea, pain, swelling, fever, itching and anorexia are common symptoms of all *Keeta Damsha*. Several synthetic and plant origin analgesic are being tested for their efficacy and potency on different animal model including hot plate, tail flick, tail clip, cold pain, filament pain, tail immersion technique, acetic acid induced writhing test, formalin induced writhing test etc. **Material and Methods:** Tail clip model and Hot plate model were selected for the present study. Eighteen Swiss albino mice had been divided in to three groups each group contain six mice. First group was negative control group; second group was test drug group while third group was standard group. Test drug was given to the group 2 for 7 days O.D. **Result:** When we performed the tail clip test, response time of group 1, 2, 3 were 4.40±1.853, 14.07±9.309, 40.68±11.759 seconds respectively. In Hot Plate model, calculated response time of group 1, 2, 3 were 2.93±0.667, 5.46±0.911, 6.04±0.857 seconds respectively. When we used Dunnett's multiple comparisons test to compare the group 1 to group 2 and group 1 to group 3, there was statistically no significant role of test drug in tail clip model and hot plate model. **Discussion and Conclusion:** No effect of *Padmak Agad* is found in tail clip model. *Padmak Agad* is effective in hot plate model but not up to significant level.

INTRODUCTION

The term *Visha* is derived from the word *Vishaad* (depression, sorrow). *Acharya Susruta* in *Kalpa Sthana* of *Susruta Samhita*, and *Acharya Vagbhata* in *Uttar tantra* of *Ashtanga Hridaya*, moreover other classics and regional texts had recited concerning the origin of *Visha*. *Acharya Sushrut* has described about *Keetas* in 8th chapter of *Kalp Sthana.* According to *Acharya Vagbhatta*, heaviness in head and eyes, coma, dizziness, dyspnoea, pain, swelling, fever, itching and anorexia are common symptoms of all *Keeta Damsha*[1].

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Pain is a main symptom in all insect bites. According to the International Association for the Study of Pain (IASP), pain is defined as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage". Pain may be either physical or mental; it depends on its source of origin. Generally, mental or psychic pain is treated with antipsychotic agents, which include antidepressant and anti-anxiety drugs. However, the pain generated by physical stimuli may be treated with analgesic and anti-inflammatory medicine. Analgesics are those drugs or agents, which reduce or block the sensation of pain temporarily. Common drug used for pain are opioids and non-steroidal anti-inflammatory drugs (NSAIDs). Studies have shown that opiates cause physical dependency, tolerance, and addiction while NSAIDs usually cause gastrointestinal disorders[3]. Medicinal herbs have been used for centuries for therapeutic purposes. Many of these medicinal herbs with analgesic activity had been used without any adverse effects. *Padmak Agad* is described in *Ashtang*

Hridya Uttar tantra chapter 37. It is indicated in all types of *Luta* and *Keet Visha*. *Padmak Agad* is told as *Sarvakamika* as it can be used in all types of *Keet Visha* for treating any kind of symptoms. It can be use both externally and internally. It has three main ingredients *Priyangu, Haridra,* and *Daruharidra* along with *Madhu* and *Ghrit*. Present study was aimed to evaluate the analgesic activity of *Padmak Agad* in animal models.

Pharmacological Action of the Contents of *Padmak Agad*

Name	Family	Active principles	Pharmacological action
Priyangu (*Callicarpa macrophylla* Vahl.)	Verbineceae	Caliterpenone and its monoacetate beta cytosterol	Anti-diarrhoeal, anti-pyretic
Haridra (*Curcuma longa* Linn.)	Zinziberaceae	Curcumen, Curcumin, Starch, Albuminoids	Antineoplastic, anti-bacterial, anti- inflammatory, insecticidal activity, anti-oxidant, antifungal, analgesic
Daruharidra (*Berberis aristata* Dc.)	Berberidaceae	Berbamine, Berberin, oxycanthine, Berbarubine, palmatine, jatororrhizine, Columbamine, Hydrastin	Antimicrobial, hepatoprotective, anti-depressant, immunomodulatory

MATERIAL AND METHOD

Place of Study: Bilwal Medchem and Research Laboratory Pvt. Limited, Reengus, Sikar, Rajasthan.

Plant Material: All the three drugs were collected from different sources. (*Priyangu* was collected from Nepali Farm, Dheradun; *Haridra* was collected from Rishikul Campus, Haridwar; *Daruharidra* was collected from Betaal Ghat, Nainital). All the selected plants were identified and verified by the eminent experts of Dravyaguna Dept. at Rishikul Campus, Haridwar (UAU) with reference no. DG/RC/UAU-82. *Priyangu* fruits, *Haridra* tuber and *Daruharidra* root and stem barks were crushed into coarse powder with the help of mixer grinder. Obtained powder was sifted through sieve no. 44 and kept in air-tight container for further use.


***Priyangu* (Fresh and Dry Fruits)**

Haridra

Daruharidra

Animals

Mature swiss albino mice (wt. 25-45gm) of both sexes obtained from Bilwal Medchem and Research Laboratory Pvt. Ltd were used for the experiment. The animals were housed under standard laboratory conditions at room temperature with relative humidity of 70–80%. They were fed with standard commercial diet and water ad libitum. All animals had been acclimatized for at least a period of Seven days. Prior to the experiment, the animals were fasted for 12 h with water given ad libitum and weighed. All procedures described were reviewed and approved by Institutional Animal Ethics Committee (IAEC) (BMRL/AD/CPCSEA/IAEC/2022/7/2)

Preparation and Administration of Test drug

Dose formulation was achieved by mixing the test formulation vehicle (CMC 2%) at the desired concentration. Dose formulation(s) had been prepared shortly prior to administration. Oral dosing had been achieved by oral feeding needle using an intubation needle fitted with a graduated syringe.

Study Design

The animals were randomly selected in 3 groups of 6 mice each. Mice were marked with Picric acid as H (mark on head), B (mark on back), T (mark on tail), HB (mark on head and back), BT (mark on back and tail) and HT (mark on head and tail) for individual identification, and kept in their cages. Group

1 was negative control group which had received CMC solution 5ml/kg/P.O. Group 2 was test group which had received *Padmak Agad* in the dose of 130mg/kg/ P.O for 7days. Group 3 was Standard Group which had been received Diclofenac 25mg/kg/P.O. CMC (1%), Test sample (20%w/v) and Diclofenac (2.5%w/v) solution had been administer orally with help of oral feeding needle.

Dosing Chart

Group 1 (Negative control)		
Marking	**Weight (gm)**	**Dose of CMC (1%) 5ml/kg**
H	40.82	0.204
B	36.72	0.184
T	44.91	0.224
HB	34.49	0.172
BT	31.78	0.159
HT	37.10	0.185

Group 2 (Test Group)			
Marking	**Weight (gm)**	**Test Sample (130mg/kg) @ 20 % solution**	
		Dose in mg	**Dose in ml**
H	44.03	57.239	0.0286
B	28.53	37.089	0.0185
T	39.05	50.765	0.0254
HB	30.95	40.235	0.0201
BT	42.72	55.536	0.0277
HT	35.37	45.981	0.0229

Group 3 (Standard Control)			
Marking	**Weight (gm)**	**Diclofenac (25mg/kg) @ 2.5% solution**	
		Dose in mg	**Dose in ml**
H	37.97	0.9492	0.038
B	44.04	1.101	0.044
T	29.70	0.7425	0.030
HB	32.43	0.8107	0.032
BT	33.31	0.8377	0.033
HT	28.07	0.7017	0.028

Haffner's Tail Clip Model- An artery clip was applied to the root of the tail (approximately 1cm away from the body) to induce pain. The animal responded quickly to this noxious stimulus by biting the clip or tail near the clip site. The time between the onset of the stimulus and the response was measured with a stopwatch in 1/10 increments. The maximum reaction time was fixed at 60 sec to prevent any tail tissue injury. If the reading exceeds 60 sec, it would be considered as maximum analgesia.


Hot Plate Model

The hot plate, which is commercially available, consists of an electrically heated surface. This plate can be a made up of copper or a heated glass surface. The temperature was controlled for 55° C to 56°C. The animals were placed on the hot plate and the time until either licking or jumping occurs was recorded by a stop-watch. To avoid any harm to the paw tissues, the maximum reaction time was set at 60 seconds. The reading would be deemed to have maximum analgesia if it was longer than 60 seconds.

Statistical Analysis

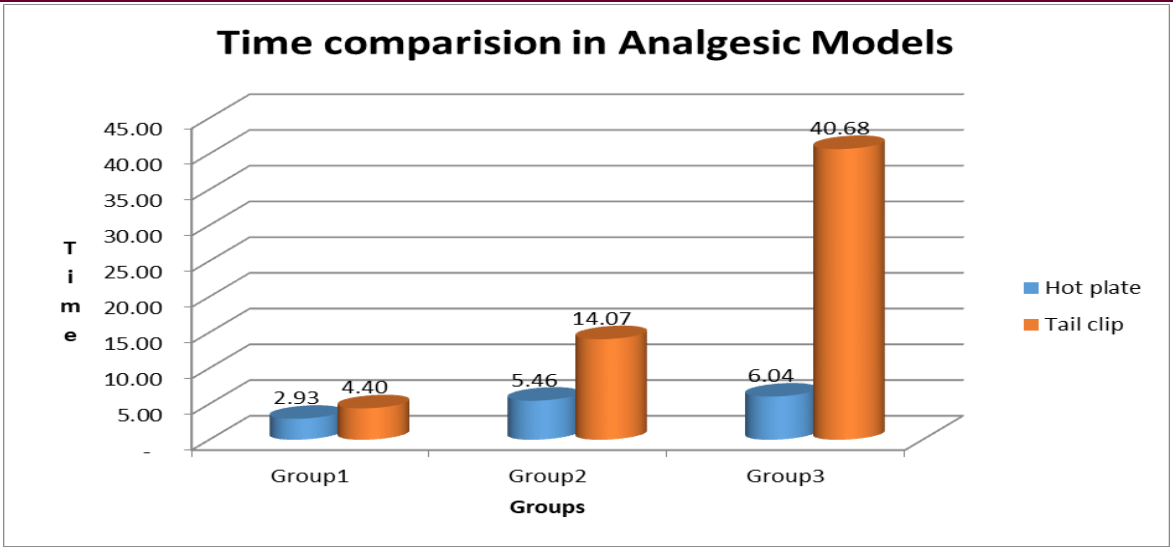
All the values were expressed as mean ± standard error of the mean (S.E.M) of six animals each across the groups. Statistical analysis of data was carried out using one-way analysis of variance (ANOVA) with help of Dunnett's multiple comparisons test. Statistically, P value <0.05 was considered to be significant.

OBSERVATIONS AND RESULT

Tail Clip (response time in sec)			
Marking	**Group 1**	**Group 2**	**Group 3**
H	2.27	11.98	57
B	4.1	4.38	5.02
T	2.35	60	60
HB	1.52	2	60
BT	13.5	1.81	60
HT	2.65	4.25	2.07

Hot plate (response time in sec)			
Marking	**Group 1**	**Group 2**	**Group 3**
H	6.1	8.12	7.83
B	2.25	2.09	2.76
T	1.85	5.51	6.1
HB	2.29	3.63	8.54
BT	3.26	6.84	4.72
HT	1.85	6.56	6.27

In-vivo Analgesis Activity	**Group 1 Mean±SEM**	**Group 2 Mean±SEM**	**Group 3 Mean±SEM**
Tail Clip (response time in sec)	4.40±1.853	14.07±9.309	40.68±11.759
Hot plate (response time in sec)	2.93±0.667	5.46±0.911	6.04±0.857



Statistical Analysis

Tail Clip					
Dunnett's multiple comparisonstest	**Mean Diff.**	**95.00% CI of diff.**	**Significant ?**	**Summary**	**Adjusted P Value**
Group 1 vs. Group 2	-9.672	-39.77 to 20.43	No	ns	0.6571
Group 1 vs. Group 3	-36.28	-66.38 to -6.184	Yes	*	0.0187

Hot plate					
Dunnett's multiple comparisonstest	**Mean Diff.**	**95.00% CI of diff.**	**Significant?**	**Summary**	**Adjusted P Value**
Group 1 vs. Group 2	-2.525	-5.348 to 0.2981	No	ns	0.0811
Group 1 vs. Group 3	-3.103	-5.926 to -0.2803	Yes	*	0.0313

DISCUSSION

Analgesics are medications that selectively affect the central or peripheral nervous system to block pain signals without severely affecting consciousness [4]. Raising the pain threshold and changing the body's physiological reaction to pain are two ways that centrally acting analgesics work. On the other hand, peripherally acting analgesics work by preventing impulses from being generated at the pain's chemoreceptor site [5]. There are a number of ways to gauge central analgesic activity, including the tail-clip and hot plate. The animal models employed for screening of analgesic activity in this study were pain-state models using thermal stimuli (which include hot plate methods) and mechanical stimuli (which include Heffner's tail clip model). Both the models are useful in illustrating centrally mediated anti-nociceptive responses which focus generally on changes above the spinal cord level. The tail clip method mediates a spinal reflex to a nociceptive stimulus while hot plate method involves higher brain functions and is regarded a supraspinally organized response. Diclofenac was used as reference drugs, which is considered mild to moderate analgesics. The failure of the CMC solution of test drug to inhibit these behaviors on tail clip method indicates that it might not be centrally acting. Hot plate method produces measureable behavioral components in response to thermal pain, with regard to their reaction times. Paw licking and jumping responses in rats are considered to be integrated supraspinally. Thus, the positive result of CMC solution of *Padmak Agad* against these behaviors on hot plate method indicates that it might be acting at supraspinal level. Analgesic drugs which are supraspinally acting elevate pain threshold of animals towards heat. Therefore, the analgesic effect of the *Padmak Agad* on this pain-state model indicates that it might be acting supraspinally. Taken together, hot plate is a better method to evaluate analgesic activity compared to tail clip method, as no significant results were observed for the treatments using tail clip method. Although hot plate model showed positive result to the test drug but on applying Dunnett's multiple comparisons test, there was statistically insignificant results of test drug group (*Padmak Agad*) in comparison to standard drug group in both the models.

CONCLUSION

Whole experimental protocol was approved from IAEC (Institutional Animal Ethics Committee) and whole experiment was performed under the guidelines of CPCSEA (Committee for Purpose of Control and Supervision of Experiments on Animals). Swiss Albino mice were selected for analgesic study. No analgesic effect of *Padmak Agad* was found in tail clip model. *Padmak Agad* was found effective in hot plate model but not up to significant level. So in our study on analgesic role of *Padmak Agad*, the null hypothesis; i.e. there is no role of *Padmak Agad* as an analgesic; is approved. If we change the model of study or the mode of administration of drug, it is possible that we can get better results in future.

This preliminary study did not fully demonstrate the dose-dependent analgesic effect of the CMC solution of *Padmak Agad* which remains a limitation of the present study. Future research may focus on determining whether the analgesic effect was dose-dependent and whether other animal models, such as the acetic acid-induced abdominal contraction test or the writhing assay for the assessment of peripheral antinociceptive activity, were applicable.

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