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Research Article

Comparative In Vivo And Clinical Study Of Karamardadi Tablet And Diclofenac Sodium Tablet In Post Haemorrhoidectomy Pain Management In Wister albino Rats

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ABSTRACT:

Background: Karamard (*Carissa carandas*) is species of flowering shrub with Apocynaceae family with black sweet or sour fruits abundant in high temperature regions rich in Iron, vitamin C, Calcium and Vitamin A. Its fruits are used in Ayurveda to treat acidity, skin rashes, fever. ¹The present herbal compound i.e. KARMARDADI YOGA is in practice for analgesia which relieves pain, which could be used to supplement anesthesia as well as get rid of adverse effect of modern analgesic drug.

Objectives: The present investigation in Wistar Albino Rat is to evaluate the Preclinical safety of Karamardadi tablet. And also investigate an analgesic effect of Karamardadi tablet in wister albino rats.

Materials and methods: For acute toxicity study one group consisting 03 animals (2 groups). The test item has been administered orally at a dose of 2000mg/kg on day one of the experiment.

For analgesic effect, Male albino wistar rats 150-200g are divided into five groups, each group consisting of six rats. A tail flick analgesia meter is used for this test.

Results: It is observed that oral administration higher doses of karmardadi tablet for 21 days led to a notable elevation in the pain threshold, demonstrating a significant increase comparable to that achieved with Diclofenac sodium. This suggests promising potential for the extracts as potent analgesics.

Conclusion: There was no mortality observed in rat after administration of test items once at a dose of 2000mg/kg. It could be deduced from results obtained from this study that karmardadi tablet have analgesic property in albino rats, yet emphasized the necessity for clinical trials.

Key words: Karamard (*Carissa carandas*), Apocynaceae, Diclofenac sodium, Analgesic,

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Introduction:

'Pain' is derived from the Latin word '**Ponea**' and used most commonly in medical sciences. Pain is defined by

the International Association for the Study of Pain (IASP) as an unpleasant sensory and emotional experience associated with actual or potential tissue

damage mainly due to tissue trauma², sterile inflammation and tissue hypoxia but at times may be due infection which is bacterial in nature . It starts with the surgical tissue trauma and ends with healing. Post operative pain is a clinical variant of acute pain produced by surgery and persists until healing has occurred. It is clear that stress response of post-operative period is harmful and may be related to increase morbidity, mortality also present the development of chronic pain states. So it requires potent analgesic like pharmacological techniques or physiological methods. Uncontrolled pain may cause struggling, crying, and restlessness this can result in hematoma formation and thereby delay in wound healing. Adequate pain control leads to decreased manipulation of the surgical site and thus reduces swelling, hematoma formation, and infection³. So it is necessary to control post operative pain. Most of analgesics produce a potent analgesic action but none of them are devoid of their known systemic untoward effects and hence are used with certain limitations.

In the text of Ayurveda a large number of drugs are mentioned under the heading *Vedanasthapan*, *Shothahara*, *Vatashamaka* and *Shoolaprashamana* groups and at different places with their specific analgesic actions⁴ Ayurvedic drug which relieve pain could be used to supplement anesthesia as well as get rid of adverse effect of modern drug.⁵

KARMARDADI YOGA which is combination of *Jati*, *Karmarda* and *Kanji*. According to Ayurvedic literatures *Jati* (*jasminum officinilis* linn.) is *tridosahara* and indicated in *shir,mukha* and *danta arti*, *Karmarda* (*Carissa carandas*) is *vathara*⁶ and *Kanji* is also having *vata* and *kapha* har property⁷. Chemically *Jati* and *Karmarda* contains salicylic acid. *Kanji* which is one of sandhan kalpana i.e. fermented preparation which contains are similar to vinegar mainly acetic acid^{8,9}. By combination of salicylic acid and acetic anhydride we get acetylsalicylic acid which is one of the NSAID i.e. Aspirin⁹. So on the bases of ayurvedic references about *vathara* properties of these drugs and reverse pharmacology of these drugs this study is taken to provide clinical evidence of analgesic property of KARMARDADI YOGA with comparison with Diclofenac sodium.

This study reports the analgesic activity and acute toxicity study of karmardadi tablet in post hemorrhoidectomy pain in wister albino rats.

Material and methods: ¹⁰

Age & weight of animals:

Were seven weeks Wistar rat of age at the commencement of treatment, the weight variation of the animals not exceeded ± 20 % of the mean body weight in each sex.

Source of animals:

The animals used in this study were obtained from National Institute of Biosciences 69, At Post Dhangawadi, Off Pune- Bangalore Highway Tal: Bhore Dist: Pune 412205 1091/GO/BT/S/07/CPCSEA

Rationale for the selection of Wistar albino rat as the test system:

Wistar Rat are one of the recommended species as test system for preclinical studies. They have been widely used throughout the industry for the evaluation of product efficacy. Extensive data available for comparative purpose.

Route of administration and reason for choice:

Oral route has been chosen for administration of test sample on rats because it is the proposed route of administration to humans.

The Oral route is one of the proposed routes for toxicity testing.

Animal husbandry:

The animals were housed in sterilized polycarbonate cages. Animal rooms were maintained under standard animal husbandry conditions. The temperature of the animal room was maintained at 22 ± 3 degree C and relative humidity 30 to 70%. The photoperiodicity of 12 hours light and 12 hours dark cycle was maintained.

Feed and water:

The animals were fed on pelleted feed containing standard composition of all macro and micronutrients. Purified water collected through aqua guard was provided to animals *adlibitum*.

Identification of animals:

Animals were identified by marking. Each cage was identified with individual cage tags indicating study number, animal numbers, dose, group, route, species, sex and experiment start and end dates.

Groups:

For acute toxicity study:

Group	Sample	No of animals
1	Karmardadi tablet	3
2	Karmardadi tablet	3

For analgesic activity:

Control (Rat received 10ml/kg Normal saline PO)

Standard (Rat received 15mg/kg diclofenac sodium PO)

Treatment group1 (low dose - 200mg/kg karmardaditabket PO)

Treatment group2 (medium dose - 400mg/kg karmardaditabket PO)

Treatment group3 (high dose-600mg/kg karmardaditabket PO)

Study design:

For acute toxicity study: The single dose toxicity study design involves consisting 06 Animals. The feed intake and body weight of the animals were recorded weekly once during the experimental period.

For analgesic activity: Adult male Wistar albino rats (2–3-month-old) weighing 200-220 g were placed in cages with constant temperature ($24-27^{\circ}\text{C}$), constant relative humidity (50%- 70%), and controlled light (12 h light/dark). All rats were fed standard laboratory diets

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and given water ad libitum. Animals were acclimatized and quarantined for at least two weeks before experiment. This study was carried out in accordance with CCSEA and an experimental protocol approved by the research ethics committee at Biocyte institute of research and development, Sangli with the serial number IAEC/sangli/2022-23/08 and the exact date of approval 11th October 2023

Induction of pain in rats:

Pain was induced by tail flick method, which cause heat stimulation in rat tail. Vehicle, standard and the test were administered to respective group of animals. A tail flick analgesia meter is used for this test. The instrument consists of an arrangement of exposing the middle part of the tail of the restrained rat to a point source of radiant heat. The animal withdraws its tail in response to heat applied. The reaction time of this movement is known as tail flick latency. A

prolongation of reaction time is adjudged as an analgesic activity. The instrument automatically records the reaction time and the heat source is simultaneously switched off. A cut off time of 15 seconds was set to avoid damage to the tail of animal. Animals that show mean retention time more than 15 sec. were not included in the study. The tail flick latency was recorded prior to drug administration and at 30, 60 and 90 min. after drug administration.

Observations with results:

In Acute toxicity study:

PRE-TERMINAL DEATHS:

The animals were observed frequently (30min, 1hr, 2hr and 4hr) after exposure to the test item and every day twice for 14 days to record the symptoms of toxicity and mortality, if any. There were no preterminal deaths observed during study period (Table-I).

TABLE – I PRE-TERMINAL DEATH(S) 1 karmardadi:

Sex	Animal no.	Day													
		1	2	3	4	5	6	7	8	9	10	11	12	13	14
Females	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	3	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Males	4	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	5	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	6	0		0	0	0	0	0	0	0	0	0	0	0	0

0-Normal: X-Not survive

PHYSIOLOGICAL ACTIVITY:

Food intake : The food intake profile was recorded once a week during the experimental period. The food intake was found to be normal and no significant effect was seen in the animals during the study period.
Body weights: The body weight of each animal was recorded once a week during the experimental period. The body weight gain was normal and no significant effect was seen in the animals during the study period

CLINICAL OBSERVATIONS:

The animals were observed once during the first 30 min and during the first four hours after exposure to the test item. The clinical signs, if any were recorded for 14 days.
There were no changes in the clinical observations and the observations include gross evaluation of skin, fur, eyes, mucous membranes, respiratory, salivation, diarrhea, behavioral pattern, autonomic and central nervous systems. Particular attention was directed to observations of tremors, convulsions, and coma.

TABLE – II CLINICAL SIGNS Karamardadi:

General signs	1	2	3	4	5	6
Signs of convulsion limb paralysis)	0	0	0	0	0	0
Body tone	0	0	0	0	0	0
Lacrimation	Y	Y	Y	Y	Y	Y
Salivation	Y	Y	Y	Y	Y	Y
Tremour	0	0	0	0	0	0
Change in skin colour	Y	Y	Y	Y	Y	y
Piloerection	Y	Y	Y	Y	Y	y
Defecation	0	0	0	0	0	0
Sensitivity response	0	0	0	0	0	0
Locomotion muscle	0	0	0	0	0	0
Gripness	0	0	0	0	0	0
Rearing	0	0	0	0	0	0
Food intake	0	0	0	0	0	0

0-Normal: X-Not survived: Y-No any sign

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TABLE III - FOOD INTAKE

Animal id	Day	
	0	14
01	121 gm	133 gm
02		
03		
04		
05		
06		

TABLE IV - BODY WEIGHT

Animal id	Day	
	0	14
01	189gm	209 gm
02	203 gm	219 gm
03	187 gm	205 gm
04	188 gm	213gm
05	193 gm	208 gm
06	198 gm	214 gm

Evaluation for analgesic effect:

%Analgesia=MPE=TL-BL/ML-BL× 100

MPE =Maximum possible effect

ML=Maximum latency or cut off time TL = Test latency

BL= Basal latency

TAIL WITHDRAWAL LATENCY:

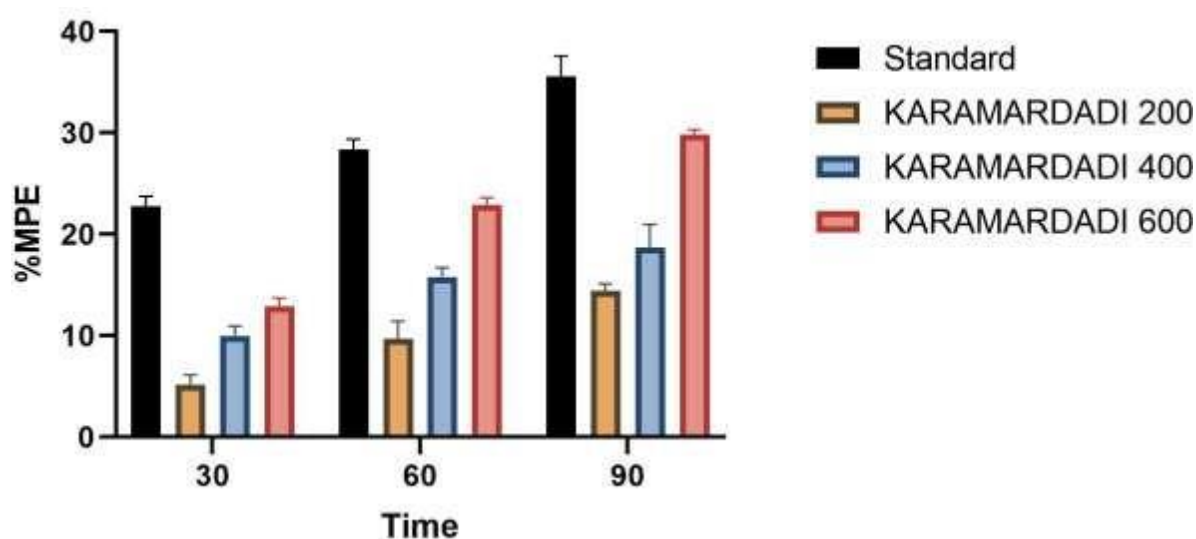
TREATMEN T	ANIMA LS	WITHDRAWAL TIME IN SEC. AFTER DRUG ADMINISTRATION			
		BASAL TIME	30 Min.	60 min.	90 min.
CONTROL	1	3.21	3.34	3.21	3.17
	2	2.92	2.97	3.05	3.23
	3	3.23	3.45	3.47	3.21
	4	3.31	2.97	3.10	3.45
	5	3.12	3.42	3.01	3.68
	6	2.95	2.98	3.11	3.27
STANDARD	1	3.83	6.43	6.84	7.35
	2	3.67	5.98	6.41	6.90
	3	3.14	5.47	6.62	7.45
	4	3.21	6.10	6.83	7.97
	5	3.34	6.01	6.71	7.42
	6	2.99	6.11	6.62	7.98
KARAMARD ADI (200 mg/kg)	1	2.93	3.92	4.95	5.04
	2	3.40	4.30	4.53	5.11
	3	3.32	3.64	3.91	4.88
	4	2.98	3.35	3.98	4.65
	5	3.43	4.03	4.81	5.05
	6	3.37	3.85	4.11	4.90
KARAMARD ADI (400 mg/kg)	1	3.05	4.78	5.35	5.60
	2	4.01	4.97	5.67	5.95
	3	3.43	4.35	4.97	5.21
	4	3.51	4.47	5.12	5.52
	5	3.23	4.52	5.01	5.68
	6	2.95	4.08	5.11	5.32
KARAMARD ADI (600 mg/kg)	1	3.31	4.95	6.04	6.54
	2	3.46	5.34	6.38	7.01
	3	3.18	4.45	5.98	6.75
	4	3.23	4.63	5.81	6.62
	5	3.47	4.95	5.77	6.98
	6	3.51	4.83	6.15	7.07

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PERCENTAGE ANALGESIA (in%):

GROUP	ANIMAL	AT 30 min.	AT 60 min.	AT 90 min.
STANDARD	1	23.28	26.95	31.51
	2	20.39	24.18	28.50
	3	19.65	29.34	36.34
	4	24.51	30.70	40.37
	5	22.90	28.90	34.99
	6	25.98	30.22	41.54
KARAMARDADI (200 mg/kg)	1	8.20	16.74	17.55
	2	7.76	9.74	14.74
	3	2.74	5.05	13.35
	4	3.08	8.32	13.89
	5	5.19	11.93	14.00
	6	4.13	6.36	13.15
KARAMARDADI (400 mg/kg)	1	14.48	19.25	21.33
	2	8.74	15.10	17.65
	3	7.95	13.31	15.38
	4	8.36	14.01	17.49
	5	10.96	15.12	20.81
	6	9.38	17.93	19.66
KARAMARDADI (600 mg/kg)	1	14.03	23.35	27.63
	2	16.29	25.30	30.76
	3	10.74	23.69	30.20
	4	11.89	21.92	28.80
	5	12.84	19.95	30.44
	6	11.49	22.98	30.98

Groups	AT30 min.	AT60 min.	AT90 min.
Control	-	-	-
Standard	22.78 ± 0.98	28.38 ± 0.99	35.54 ± 2.04
KARAMARDADI (200 mg/kg)	5.18 ± 0.95	9.69 ± 1.72	14.44 ± 0.66
KARAMARDADI (400 mg/kg)	9.97 ± 0.99	15.78 ± 0.94	18.72 ± 2.27
KARAMARDADI (600 mg/kg)	12.88 ± 0.82	22.86 ± 0.73	29.80 ± 0.53





Discussion

In this study, we utilized the tail flick method, renowned for its efficacy in evaluating the potency and effectiveness of centrally acting analgesic medications. Our findings indicate that higher doses of the extracts led to a notable elevation in the pain threshold, demonstrating a significant increase comparable to that achieved with Diclofenac sodium. This suggests a promising potential for the extracts as potent analgesics.

The tail flick method's sensitivity allowed us to discern subtle variations in analgesic efficacy. These results underscore the importance of dosage in eliciting therapeutic effects. Moreover, the comparability to Diclofenac sodium highlights the potency of the extracts, suggesting their potential as alternative or complementary treatments for pain management. Further investigation into the underlying mechanisms and long-term effects of these extracts is warranted to validate their clinical utility fully.

Limitations of this study

Limitations of the study in the present study, we did not investigate the active principle responsible for the analgesic activity of the Karamardadi's.

Conclusion:

There were no clinical symptoms of toxicity and mortalities observed in all treated group animals after single dose (2000mg/kg) administration of test item once.

- Food intake and Body weight gain was normal in all the animals.
- There were no significant changes observed in physical, physiological and behavioral profile of the animals.

The study endorsed Karamardadi's efficacy in treating painful conditions, yet emphasized the necessity for clinical trials. Further research is imperative to pinpoint the specific active ingredient, potentially leading to the creation of potent analgesic medications. Identifying these active principles could pave the way for more targeted and effective pain management strategies.

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