

Evaluation of Anti-Inflammatory, Analgesic and Antipyretic Properties of *Neolamarckia Cadamba* on Wistar Albino Rats



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Abstract

This Research Article focused on anti-inflammatory, analgesic and antipyretic activity of *Neolamarckia cadamba* leaf extract in order to evaluate the effect of ethanolic extract of *Neolamarckia cadamba* (Family: Rubiaceae) leaves showed significant anti-inflammatory, analgesic and antipyretic activity. The acute toxicity, orally evaluated in Rats, was found to be higher than 2000mg/kg. The antinociceptive response using tail flick and hot plate Method in rats were examined. The anti-inflammatory activity using carrageenan and antipyretic activity in yeast induced pyrexia in rats, were also examined. The extract at the dose 400mg/kg significantly reduced the numbers of pain but the extract significantly exerted protective effects on heat-induced pain in rat at all tested doses (lower dose 200mg/kg and high dose 400mg/kg p.o.). The percentage inhibition of oedema due to injection of carrageenan was found to be in accordance with the doses tested. The extract showed significant effect on yeast-induced fever in rats at higher dose of 400mg/kg and no promising results with 200 mg/kg lower dose level. It was observed that high dose of *Neolamarckia cadamba* extract showed greater decrease in analgesic, anti-inflammatory and antipyretic activity in comparison to the control group rats. Although these results provide a support for the traditional uses of *Neolamarckia cadamba* leaves, further studies are necessary to better evaluate its safety and modes of action.

Keywords: *Neolamarckia Cadamba*; Leaf; Analgesic; Anti-inflammatory; Antipyretic activity

Abbreviations: N. Cadamba: *Neolamarckia Cadamba*; NISCAIR: National Institute of Science Communication and Information Resources; CSIR: Council of Scientific & Industrial Research; EENC: Ethanolic Extract of *Neolamarckia Cadamba*

Introduction

Neolamarckia cadamba (Roxb) Bosser, syn. *Anthocephalus cadamba* var. *A. chinensis* (Rubiaceae) commonly known as Kadam is a large tree up to 45m high, frequently found in moist deciduous evergreen forests and widely distributed throughout the greater part of India [1]. Leaves glossy, dark green, opposite, simple pulvinus base sub sessile to petiolate, broadly ovate to elliptical-oblong, entire, apex marinate and venation pinnate. The flowers that appear from August to October are orange to yellow. The bark is gray, smooth in young trees, rough and longitudinally fissured in old trees [2]. The dried leaf is used as folk medicine in the treatment of anemia, uterine complaints and for improvement of semen quality and reported to possess astringent, mucolytic, analgesic, febrifuge and antiseptic properties. However, only a few phytochemical and pharmacological or biological test reports have been reported on this plant in the literature. Chlorogenic acid isolated from the leaf has been reported to possess hepatoprotective activity and lipid peroxidation in liver microsomes [3]. In the present study, we investigated the anti-

inflammatory activity of the ethanolic extract of *N. cadamba* leaves in experimental animal model using carrageenan-induced paw edema in rats (Figure 3). The analgesic and antipyretic activities were also examined using the hot plate method, tail flick method in rats and yeast-induced pyrexia in rats respectively (Figure 1, 2, 4).

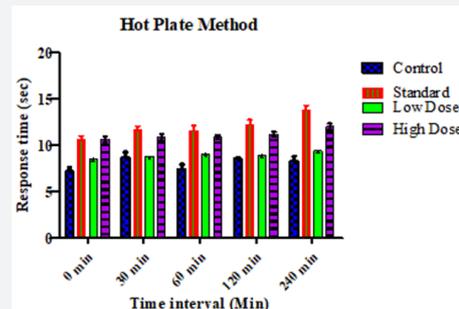


Figure 1: Effect of *Neolamarckia Cadamba* on Hot plate method in rats.

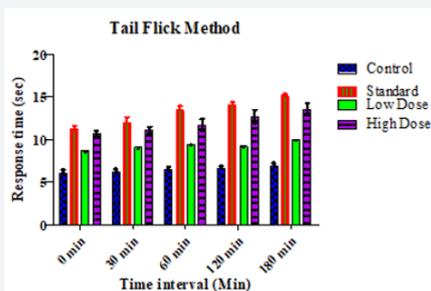


Figure 2: Effect of *Neolamarckia Cadamba* in TFM in rats.

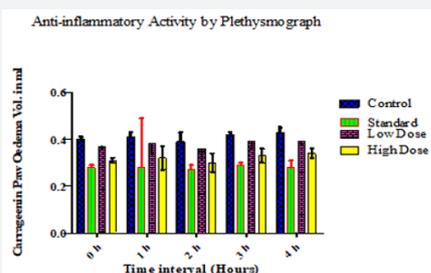


Figure 3: Effect of *Neolamarckia Cadamba* Anti-Inflammatory Activity by Carrageenan Induce Paw Oedema in rats.

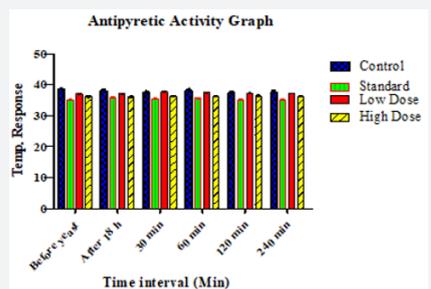


Figure 4: Effect of *Neolamarckia Cadamba* Antipyretic Activity by Brewer's Yeast Induce Pyrexia in rats.

Material and Methods

Plant material collection and identification of plant

The leaves of the *Neolamarckia cadamba* were collected from Monad University Hapur, Uttar Pradesh. For authentication, it was made an herbarium in which plant part are attached. Then it was authenticated from the taxonomist of NISCAIR, NEW DELHI. Ref. No- NISCAIR/RHMD/Consult/2018/3242-43 by Mr. RS Jayasomu (Senior Principal Scientist Head, RHMD) and Dr. Sunita Garg (Emeritus Scientist, CSIR-NISCAIR).

Preparation of extraction of neolamarckia cadamba

The plant materials of *Neolamarckia cadamba* leaves washed with tap water, shade dried at room temperature and powdered by an electrical blender. From each sample, 100g of the plant materials were extracted with 300ml of organic solvent Ethanol for 24hrs in a soxhlet apparatus. The crude plant extracts were evaporated to dryness in rotary vacuum evaporator. Phytochemical screenings

of extracts were subjected to various qualitative chemical tests to screen for phytochemical constituents [4].

Experimental animals

Wistar albino rats (150-250gm) were procured from School of Pharmacy, Monad University animal house. All animals were housed in a group of 4 in polypropylene cages under standard housing conditions (12:12h) light and dark cycle, temperature 22 ± 2 °c and humidity $45 \pm 5\%$) with standard feed pellet and free access to water ad libitum. Standard hygienic conditions were maintained. The animal committee (SOP, MU/IAEC/2018) and by the animal regulatory body of government [5]. After three weeks of acclimatization, animal was used for the following studies and divided into the four groups. Four groups were made each containing six animals and named as Figure 3.

1. Group I: Control (sterile water)
2. Group II: Standard Aspirin (200mg/kg i.p)
3. Group III: Low dose of EENC (200mg/kg p.o)
4. Group IV: High dose of EENC (400mg/kg p.o)

Acute toxicity study

The acute toxicity studies were conducted as per OECD guidelines 420, where the limit test dose of 2000mg/kg, p.o., used. Observations were made and recorded continuously for the first 4h for any behavioral changes. They were then kept under observation up to 14 days after drug administration to find out the mortality [6].

Evaluation of analgesic activity by Hot plate method:

The method was performed according to [7]. Rats were placed on a hot plate maintained at temperature of 50 ± 10 . The time taken for either paw licking or jumping (pain reaction time) by each rat was recorded. Rats that showed initial nociceptive response within 20 seconds were selected and used for the study. The rats were then divided into 4 groups of 6 rats per group. Group I served as negative control, while group II received Aspirin 200mg per kg (i.p) and III, IV group received extract (p.o) at dose 200mg and 400mg per kg respectively to act as positive control. Thirty minutes later each rat was placed on a hot plate and the pain reaction time recorded [7] Figure 4.

Evaluation of analgesic activity by Tail flick method

The method was performed according to [8]. Most commonly, an intense light beam is focused on the animal's tail and a timer starts. When the animal flicks its tail, the timer stops and the recorded time (latency) is a measure of the pain threshold. Alternate methods can be used to apply heat. Alternately, a dolorimeter with a resistance wire with a constant heat flow may be used. For the tail flick method, the wire is attached to the tail of the organism, and the wire applies heat to the tail then records the latency to tail flick [8].

Evaluation of Anti-Inflammatory Activity by Carrageenan Induce Paw Oedema

The method was performed according to [8]. The animals were divided into four groups. The control group were given the vehicle through oral route. Other groups were received aspirin or the test extract in a similar manner. Carrageenan was administered to the rats into the planter surface of the right hind limb to induce paw oedema. Paw volume was measured with a Plethysmograph after 1, 2, 3 and 4h of carrageenan injection and paw swellings was compared with control. Percentage inhibition of oedema was calculated [8].

Evaluation of Antipyretic Activity by Brewer's Yeast Induce Pyrexia

The antipyretic activity was evaluated using Brewer's yeast-induce pyrexia in rats. Fever was induced by injecting 10ml/kg (s. c.) of 20% aqueous suspension of Brewer's yeast in normal saline i.e. Eighteen hours after the injection, the rectal temperature of each rat was measured using a digital thermometer. Only rats that showed an increase in temperature were selected for the study and animals were divided into four groups. The groups of animals receive one of the following in a similar manner: Aspirin and test

extracts. The rectal temperature was measured at 1, 2, 3 and 4h after treatment [9].

Results

Preliminary phytochemical tests revealed presence of alkaloids, Glycosides, Proteins, Amino Acid, Carbohydrates, flavonoids, tannins and phenolic compounds in the ethanol extract of *N. cadamba*.

Acute toxicity study

When orally administered to Rats in graded doses from 100 to 2000mg/kg, the ethanol extract produced sedation and analgesia at all tested doses. However, there was no mortality in any of the above doses at the end of the 14 days of observation [10].

Effect of ethanolic extract of *N. cadamba* and aspirin on nociceptive response induced by heat in Rats

The ethanolic extract of *N. cadamba* Leafs at the dose 400mg/kg significantly reduced the numbers of pain induced by Hot plate in Rats. But the extract at 200mg/kg p.o. did not elicit significant response. However, the reference drug aspirin (200mg/kg) produced significant protective effects. (Table 1).

Table 1: Effect of ethanolic extract of *Neolamarckia Cadamba* and Aspirin on Hot Plate Method in Wistar Rats.

Serial No.	Treatment	Duration of Latency of Jumping Response in (sec) at Various Time Intervals				
		0h	1h	2h	3h	4h
1.	Control	7.23±0.40	8.70±0.46	7.45±0.49	8.58±0.15	8.31±0.52
2.	Standard Aspirin (200mg/kg)	10.59±0.42***	11.66±0.23***	11.58±0.54***	12.25±0.50***	13.86±0.38***
3.	EENC (200mg/kg)	8.54±0.26**	8.83±0.22**	9.11±0.20**	8.96±0.27***	9.41±0.22***
4.	EENC (400mg/kg)	10.65±0.34***	10.87±0.37***	10.88±0.38***	11.21±0.26***	12.03±0.18***

Effect of ethanolic extract of *N. cadamba* and aspirin on nociceptive response induced heat by tail flick in Rats.

Table 2: Effect of ethanolic extract of *Neolamarckia Cadamba* and Aspirin on tail flick method in rats.

Sr. No.	Treatment	Duration of Latency of Tail Flick Response in (sec) at Various Time Intervals				
		0 min	30 min	60 min	120 min	180 min
1.	Control	6.00± 0.42	6.20± 0.34	6.45± 0.34	6.64±0.26	6.94± 0.32
2.	Aspirin (200mg/kg)	11.20±0.43***	12.01±0.62***	13.47±0.47***	14.04±0.42***	15.14±0.23***
3.	EENC (200mg/kg)	8.72 ±0.16**	9.08 ± 0.18**	9.44 ±0.14**	9.21± 0.11**	10.00± 0.11**
4.	EENC (400mg/kg)	10.73±0.32***	11.12 ±0.41***	11.73±0.69***	12.71±0.77***	13.55±0.74***

The mean latency of nociceptive responses to thermal stimuli in the tail flick method is summarized in Table 2. The ethanolic extract of *N. cadamba* leaf exhibited significant response at all tested dose levels in a dose dependant manner that is comparable

with response of the standard drug aspirin. The extract significantly exerted protective effects on heat-induced pain in Rats (Table 2).

Table 3: Effect of ethanolic extract of *Neolamarckia Cadamba* and Aspirin on Anti-Inflammatory Activity by Carrageenan Induce Paw Oedema in rats.

S.No.	Groups (Dose)	Percentage Inhibition of Carrageenan induced Paw Oedema (ml)								
		0h	1h	% Change	2h	% Change	3h	% Change	4 h	% Change
1.	Control	0.33±0.1	0.37±0.2	-	0.49 ± 0.04	-	0.51± 0.01	-	0.48±0.03	0.03↓
2.	Aspirin (200mg/kg)	0.32±0.01**	0.31±0.21**	0.01 ↓	0.33±0.02**	0.02 ↓	0.36 ± 0.03**	0.30 ↓	0.28±0.03**	0.08↓
3.	EENC (200mg/kg)	0.34±0.01*	0.46±0.04*	0.12 ↑	0.48 ± 0.04*	0.02 ↓	0.47 ± 0.03*	0.01 ↓	0.44±0.001*	0.03↓
4.	EENC (400mg/kg)	0.30±0.01**	0.43±0.012**	0.13 ↑	0.37±0.05**	0.06 ↓	0.34 ± 0.03**	0.04↓	0.30±0.01**	0.04↓

Effect of ethanolic extract of *N. cadamba* and aspirin on carrageenan induced paw oedema in rats

Oral administration of the ethanolic extract at the doses of 200 and 400mg/kg significantly suppressed the paw oedema at 2 and 4hr after carrageenan injection in rats. The percentage inhibition of oedema was found to be in accordance with the doses tested. Aspirin (200mg/kg), the standard control, also produced significant effect and reduced paw oedema in this test but the effects were observed from the 1h of carrageenan injection in the test animals (Table 3).

Effect of ethanolic extract of *N. cadamba* and aspirin on brewer’s yeast induced pyrexia in rats

The ethanolic extract of *N. cadamba* leaf showed significant effect on yeast-induced fever in rats at dose 400 mg/kg. The reference drug aspirin suppressed the fever induced by yeast in rats from 1st hour of drug administration. On the other hand, the ethanol extract produced significant activity at 4th hour of test sample administration and no promising results with 200mg/kg dose level (Table 4) [11-18].

Table 4: Effect of ethanolic extract of *Neolamarckia Cadamba* and Aspirin on Antipyretic Activity by Brewer’s Yeast Induce Pyrexia.

S. No.	Group (Dose)	Average Rectal Temperature (°C)					
		Before Yeast	After 18hrs (0min)	30min	60min	120min	180min
1.	Control	37.78± 05.29	38.72± 0.29	37.48± 0.28	37.54± 0.28	37.42±0.28	37.43±0.26
2.	Aspirin (100mg/kg)	36.73± 0.25**	36.72± 0.13**	36.32± 0.12**	36.16±0.06**	35.41±0.21**	35.02±0.28**
3.	EENC (200mg/kg)	37.16± 0.01*	38.5± 0.04*	37.19± 0.02*	36.94± 0.03*	36.96±0.02*	36.35±0.04*
4.	EENC (400mg/kg)	36.57± 0.16**	38.05± 0.18**	36.40± 0.21**	36.49± 0.23**	37.19±0.16**	35.48±15.29**

Discussion

The results demonstrate that the ethanolic extract obtained from *N. cadamba* leaf exhibited significant analgesic activity. The hot plate method is generally used for screening of antinociceptive effects. The tail flick method is another thermic pain model, which assesses the way an animal responds to moderate continuous pain generated by a tissue. Thermic painful stimuli are known to be selective to centrally but not peripherally acting analgesic drugs. In the present study, the ethanolic extract significantly reduced the pain in both chemical induced stimuli and thermal stimuli indicating that the constituents present in the extract possess similar mode of action as that of Aspirin. The ethanolic extract of *N. cadamba* Leaves suppressed the paw oedema induced by carrageenan in rats compared with aspirin, a nonsteroidal anti-inflammatory drug, which possesses analgesic, antipyretic and anti-inflammatory activities by inhibition of prostaglandin synthesis via Cyclooxygenase activity. Thus, the anti-inflammatory

action of the extract from *N. cadamba* leaves may act at some site of action that are similar to those of aspirin. The ethanolic extract of *N. cadamba* Leaves showed significant effect on yeast-induced fever in rats while the reference drug aspirin suppressed fever induced by yeast in rats by inhibiting the synthesis of prostaglandin E2. Although these results provide a support for the traditional uses of *N. cadamba* Leaves, further studies are necessary to better evaluate its safety and modes of action.

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