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Pharmacological Evaluation of *Mussaenda erythrophylla* Leaves Extract for Analgesic, Anti-Inflammatory, and Antipyretic Activities

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ABSTRACT

Objective: The present study aims to scientifically validate the analgesic, anti-inflammatory, and antipyretic activities of *Mussaenda erythrophylla*. **Methods:** The leaves were excised from the plant, sliced into small pieces, shade dried, and powdered. The powder was extracted with hydro alcohol, concentrated under reduced pressure and the crude extract was referred to as ME. The analgesic, anti-inflammatory, and anti-pyretic activity of ME were analyzed in Wistar rats and Swiss albino mice. **Results:** The results revealed that the hydroalcoholic extract of the leaves of *Mussaenda erythrophylla* showed a dose-dependent analgesic, anti-inflammatory, and antipyretic activity, which was comparable to the standards, Morphine, Aspirin, Indomethacin, Dexamethasone, and paracetamol respectively. **Conclusion:** The results of the current study reveal that *Mussaenda erythrophylla* possesses significant analgesic, anti-inflammatory, and antipyretic activities.

INTRODUCTION

Traditional medicine is as old as humankind and is practiced by virtually all cultures, each one with its indigenous knowledge, health practices, and benefits. In some Asian and African countries, up to 80% of the population relies on traditional medicine for their primary healthcare needs. Inflammation is a contained defensive reaction of cells/tissues of the body to allergic or chemical irritation, injury, etc. The symptoms that produced inflammation are pain, redness, heat, swelling, and failure of function that result from dilation of the blood vessels leading to an increased supply of blood and increased intracellular spaces resulting in the movement of leukocytes, protein, and fluids into the inflamed regions. Inflammatory phase inflammation may have beneficial effects such as the destruction of invading microorganisms and the walling-off of an abscess cavity to prevent the spread of disease. Analgesia is a survival mechanism that serves as a warning sign of ongoing or impending tissue damage.[1] Pain is an unpleasant sensory and produced by the excitation of particular receptors. Pain can be classified as chronic or acute. The generation of pain in response to tissue injury involves four basic elements: Transduction, Transmission, Transformation, Perception. Transduction: An occupation of nociceptors that convert noxious stimulation to nociceptive signals. Transmission: A process to send nociceptive signals along nerve fibers from the site of injury to the central nervous system (CNS). Transformation: A mechanism that modulates nociceptive signals at synaptic sites and the level of the CNS through ascending, descending, or regional facilitation and inhibition. Perception: Important component of the clinical pain experience that integrates cognitive and affective (emotional) responses.[2] Pyrexia or Fever is defined as an elevation of body temperature. It is a response due to tissue damage, inflammation, malignancy, or graft rejection. Cytokines, interleukin, interferon, and Tumor Necrosis Factor α (TNF- α) are formed in large amounts under this condition, which increases PGE2 which in turn triggers the hypothalamus to elevate body temperature. Fever is associated with symptoms of sickness behavior which consist of lethargy, depression, anorexia, sleepiness, & inability to concentrate. This increase in set-point triggers increased muscle tone & shivering. However antipyretic medication can be effective at lowering the temperature which may include the affected persons comfort.[3] According to Ayurveda, pyrexia originates from a combination of indigestion, seasonal variations, and significant alterations in daily routine. Due to poor hygiene practices and malnutrition, children in developing countries frequently suffer from various forms of infections which present as fevers. *Mussaenda erythrophylla*, commonly known as Ashanti

Blood, Red Flag Bush, and Tropical Dogwood, is an evergreen African shrub. The bracts of the shrub may have different shades, including red, rose, white, pale pink, or some mixtures. *Mussaenda erythrophylla* grows best in warmly temperate or subtropical areas and is semi-deciduous in cooler parts. In its natural habitat, the shrub may scramble up to 10 m (33 ft.) but is kept compact under cultivation. The star-like flowers of the shrub are 10 mm (0.39 in) in diameter and have a single, modified sepal. *Mussaenda erythrophylla*is native Angola, Burundi, Cabinda, Cameroon, Ivory Coast, Gabon, Ghana, Guinea, Kenya, Liberia, Nigeria, Central African Republic, Sierra Leone, Sudan, Tanganyka, Togo, Uganda, and Zaire. This is a sprawling shrub with brilliant red sepals and white flowers with red centers. In the wild, it can often climb up surrounding trees. In the garden it can be used as a sprawling shrub, 1 to 1.5 meters (3 to 4.5 feet) high by 2 to 3 meters (6 to 9 feet) wide, or be trained as a climber up support or an open foliaged tree. *Mussaenda erythrophylla* (Rubiaceae) is native to western tropical Africa, occasionally seen in gardens and parks as an ornamental plant in India, and is commonly known as mussenda (telugu), nagavalli (Sanskrit), and red flag bush (English). It is a perennial, evergreen shrub with a branched tap root system. The roots are useful for cough, jaundice, and when chewed acts as an appetizer. Several triterpenoids and glycosides were reported. Mussaenda genus viz., contains mussaendosides U(1) and V(2), mussaendosides G(1) and K(2) are two new triterpenoid saponins 4, mussaendosides A-C, M and N with cyclolanostene type aglycone and aureusidin, iridoid glycosides. The pharmacological activities reported from Mussaenda species were diuretic, antiphlogistic, antipyretic, and effective in laryngopharyngitis, acute gastroenteritis, and dysentery, and also anti-fertility activity. It is established that plants that have anti-oxidant properties exert hepatoprotective and anti-diabetic actions. It is in light of this fact that the antioxidant and free radical scavenging potential of the stem of *Mussaenda erythrophylla* (M.E) was investigated. Very recently the methanol extract of *A. leptopus* was found to possess Antithrombin activity, Antidiabetic, and consumed as food reported. The *M. Erythrophylla* roots are useful for cough, jaundice, and when chewed acts as an appetizer. The pharmacological activities reported from *Mussaenda* species were diuretic, antiphlogistic, antipyretic, and effective in laryngopharyngitis, acute gastroenteritis, and dysentery, and also antifertility activity.[4]

MATERIALS AND METHODS

Preparation of plant extract

Hydro Alcohol extract was prepared using the maceration method. The powdered *Mussaenda erythrophylla* leaves of the (50g) were macerated in 1000ml Hydroalcohol at room temperature (25°C) with occasional stirring for 7 days. After filtration with the muslin cloth, the combined aqueous extracts were evaporated in the hot plate at 30 °C and stored in desiccators for future use.

Animals

Wistar albino rats and albino mice of either sex weighing between 150 and 250 g were chosen for the study. They were housed in polypropylene cages with paddy husk bedding under controlled temperature and humidity. The animals were fed with a standard pellet diet and water *ad-libitum* as per the CPCSEA guidelines. The animal experiments were approved by Institutional Animal Ethics Committee (DAMCOP/IAEC/018).

Acute Toxicity Study

Acute toxicity study was performed as per OECD guidelines 425. Limit test 2000mg/kg was carried out to assess the toxic effect of the compound. One Swiss Albino mice of female sex were dosed 2000mg/kg compound orally in a suitable vehicle and observed for toxicity for 4 hrs. If the animal survives, additional four animals were dosed 2000mg/kg orally and observed for toxic signs. All the animals were kept under observation for 13 days after dosing. The compound is considered to be safe up to 2000mg/kg if there is no mortality among the animals.[5]

In-vivo Study

Evaluation of Analgesic Activity

Central analgesic activity – Hot plate method

The mice's paws were found to be very sensitive to heat at a temperature that is not damaging the skin. They showed responses to heat in the form of jumping, withdrawal of the paws, or the licking of the paws. The animals were placed on Eddy's hot plate kept at a temperature of 55±0.5°C. A cut-off period of 15 sec, was observed to avoid any damage to the paw. Basal

reaction time and the type of response were noted using a stopwatch. The latency was recorded at 0, 60, and 120 min after the treatment.[6]

Group1: Normal control

Group2: Standard group (Morphine 10mg/kg body weight)

Group3: Test low dose (Hydro Alcohol extract of *Mussaenda erythrophylla* of 200mg/kg)

Group4: Test high dose (Hydro Alcohol extract of *Mussaenda erythrophylla* of 400mg/kg*)*

Peripheral analgesic activity - Acetic acid-induced writhing method

Four groups of six mice each were treated with normal saline (10ml/kg) (control group), aspirin (50mg/kg), selected extract low dose, and selected extract high dose. Nociceptin was induced with the help of an intra-peritoneal (i.p.) injection of acetic acid 0.6 %, 0.1 ml/10 g body weight after 30min of treatment of extract and standard drugs. The number of stretching or writhing was recorded from 5min to 15min.[7]

Group1: Control group (normal saline 10ml/kg)

Group2: Standard group (Aspirin50mg/kg)

Group3: Test low dose (Hydro Alcohol extract of *Mussaenda erythrophylla* of 200mg/kg)

Group4: Test high dose (Hydro Alcohol extract of *Mussaenda erythrophylla* of 400mg/kg*)*

Evaluation of Anti-inflammatory Activity

Acute Anti-inflammatory studies by Carrageenan induced paw edema in rats

Animals were fasted with free access to water at least 12 hr before experiments and were randomly divided into 4 groups of six animals in each group. Edema was induced in the rat paw by injecting 0.1ml of 1% carrageenan solution in the sub-plantar region after 1 hr of treatment of extract and standard to all groups. The paw edema volume was measured with the help of a digital plethysmometer immediately at 1st, 2nd, and 5th hr after injection of carrageenan. The difference between initial and subsequent reading gave the actual edema volume.[8]

Group1: Normal control

Group2: Standard group (Indomethacin 10mg/kg)

Group3: Test low dose (Hydro Alcohol extract of *Mussaenda erythrophylla* of 200mg/kg)

Group4: Test high dose (Hydro Alcohol extract of *Mussaenda erythrophylla* of 400mg/kg*)*

Chronic Anti-inflammatory studies by Cotton pellet induced granuloma

Cotton pellets weighing 10 mg were sterilized in an autoclave for 30 min at 120°C under 15 lb pressures. Four pellets were implanted subcutaneously into the ventral region, two on either side, in each rat under light ether anesthesia. All drug doses and vehicles were administered for 7 consecutive days from the day of cotton pellet implantation. On the 8th day, the animals were anesthetized and the pellet together with the granuloma tissues was carefully removed and made free from extraneous tissues. The wet pellets were weighed for the determination of wet weight and then dried in an incubator at 60°C for 18h until a constant weight is obtained. After that, the dried pellet was weighed again. The exudates amount was calculated by subtracting the constant dry weight of the pellet from the immediate wet weight of the pellet. The granulation tissue formalin was calculated after deducting the weight of the cotton pellet from the constant dry weight of the pellet and Taken as a measure of granuloma tissue formation. The percentage inhibition of exudates and granuloma tissue formation was determined.[9]

Group1: Normal control (Distilled water)

Group2: Standard group (Dexamethazone 1mg/kg)

Group3: Test low dose (Hydro Alcohol extract of *Mussaenda erythrophylla* of 200mg/kg)

Group4: Test high dose (Hydro Alcohol extract of *Mussaenda erythrophylla* of 400mg/kg*)*

Evaluation of Antipyretic Activity

Antipyretic activity by Yeast induced Hyperthermia model

Fever in rats was induced by administration of 20%w/v of brewer's yeast in distilled water subcutaneously. Rats were induced pyrexia by injection of 10ml/kg of brewer's yeast solution under the skin in between the shoulder blades. For the spread of the suspension beneath the skin, the site of injection was thoroughly massaged. Basal rectal temperature was noted

before the injection of yeast, using a digital clinical thermometer to a depth of about 2cm into the rectum. After 18hr of yeast injection, the temperature rise was recorded. 24 febrile rats which had shown an increase in body temperature was divided into four groups of 6 animals each. Thereafter, treatment was carried out as follows:

Group1: Normal control

Group2: Standard group (Paracetamol 150mg/kg)

Group3: Test low dose (Hydro Alcohol extract of *Mussaenda erythrophylla* of 200mg/kg)

Group4: Test high dose (Hydro Alcohol extract of *Mussaenda erythrophylla* of 400mg/kg*)*

The different groups of febrile rats were orally administered with the selected extract or a standard drug, the rectal temperature was recorded at 60, 120, 180, 240 minutes after treatment. The decrease in rectal temperature after treatment indicates the antipyretic effect.[10]

RESULTS AND DISCUSSION

***In-vivo* Study**

Evaluation of Analgesic Activity

Central Analgesic Activity – Hot Plate Method

The Hydro Alcohol extract of *Mussaenda erythrophylla* exhibits a dose-dependent increase in latency time when compared with control showed in table no.1. At 120 minutes, the percent inhibition of two different doses (200 and 400 mg/kg body weight) was 42.65% & 76.24% respectively. The results were found to be statistically significant ($p<0.001$).

Table No. 1: Effect Hydro-Alcohol Extract of *Mussaenda erythrophylla* on Latency to Hot Plate Test in Mice

GROUPS	MEAN LATENCY BEFORE&AFTER DRUG ADMINISTRATION			PERCENT AGE INHIBITION	
	0 min	60min	120min	60min	120min
Control	2.26± 0.219	2.44± 0.219	2.32± 0.114	–	–
Standard	2.34± 0.088**	3.12± 0.860**	6.08± 0.529**	31.20%	52.15%
HAME 200mg/kg	2.21± 0.162**	3.61± 0.970**	8.14± 0.412**	38.18%	60.14%
HAME 400mg/kg	2.32± 0.177**	4.23± 0.381**	10.16± 0.321**	42.65%	76.24%

Results were expressed as mean ± SEM, (n=5), One way ANOVA by Dunnet test comparison between control group. The data were considered significant if * $p<0.05$, **$p<0.001$.

The hot plat test measures the complex response to a non-inflammatory, acute nociceptive input and is one of the models normally used for studying central nociceptive activity. It is a fact that any agent that causes a prolongation of the hot plate latency using this test must be acting centrally. Therefore, the HA extracts of the plants must have a central activity. Again, narcotic analgesics inhibit both peripheral and central mechanisms of pain, while NSAIDs inhibit only peripheral pain. The analgesic effect of the plants in both models suggests that they have been acting through a central and peripheral mechanism. [11]

Peripheral Analgesic Activity - Acetic Acid-Induced Writhing Method

Both doses of Hydro-Alcohol extract of *Mussaenda erythrophylla* showed significant reduction ($p<0.001$) of writhing induced by the acetic acid after oral administration in a dose-dependent manner. After oral administration of two different doses (200 and 400 mg/kg body weight), the percent inhibition was 59.90% &75.25%. The reference drug aspirin was found less potent than the plant extracts at all of the dose levels (table no.2).

Table No. 2: Effect of Hydro-Alcohol Extract of *Mussaenda erythrophylla* on Acetic Acid-Induced Writhing In Mice

GROUPS	NO OF WRITHING	PERCENTAGE INHIBITION
Control	40.40± 1.44	_
Standard	23.40± 1.71**	42.08
HAME 200mg/kg	16.20± 1.40**	59.90
HAME 400mg/kg	10.00± 0.791**	75.25

Results were expressed as mean ± SEM, (n=5), One way ANOVA by Dunnet test comparison between control group. The data were considered significant if * $p<0.05$, **$p<0.001$.

The acetic acid-induced writhing method was found effective to evaluate peripherally active analgesics. The agent reducing the number of writhing will render analgesic effect preferably by inhibition of prostaglandin synthesis, a peripheral mechanism of pain inhibition.

Evaluation of Anti-inflammatory Activity

Acute Anti-Inflammatory Studies by Carrageenan Induced Paw Edema in Rats

In the group treated with vehicle, inflammation progressively increasing up to 5 h. The animals treated with Indomethacin 10mg/kg, p.o showed significant inhibition of paw edema ($p<0.001$) up to five hours as compared to control. A high dose of test drug HAME (400 mg/kg, p.o) showed significant inhibition in carrageenan-induced paw edema ($p<0.001$) from the 3rd hour. While low dose 200 mg/kg showed significant inhibition in carrageenan-induced paw edema in rats at 5th hour ($p<0.05$). The anti-inflammatory activity of *Mussaenda erythrophylla* against carrageen-induced paw edema has been shown in (Table no. 3). And the results were comparable to that of standard drug Indomethacin.[12]

Table No. 3: Paw Volume at Different Time Interval after Carrageenan Injection

GROUPS	PAW VOLUME				PERCENTAGEIN HIBITION.
	1h	2h	3h	5h	
Control	0.22± 0.012*	0.35± 0.014*	0.33± 0.015	0.47± 0.015*	—
Standard	0.17± 0.020*	0.21± 0.018*	0.13± 0.014*	0.06± 0.013*	87%
HAME 200mg/kg	0.21± 0.008*	0.25± 0.009*	0.20± 0.012*	0.15± 0.015*	66%
HAME 400mg/kg	0.18± 0.017*	0.23± 0.012*	0.18± 0.014	0.10± 0.014	79%

Results were expressed as mean ± SEM, (n=5), One way ANOVA by Dunnet test comparison between control group. The data were considered significant if * $p<0.05$, ** $p<0.001$.

The HAME showed maximum inhibition of 66% and 83% at the dose of 200 and 400 mg/kg body wt. respectively after 3 hrs of the extract treatment against carrageenan-induced paw edema whereas the standard drug produces 87% of inhibition at the dose 10 mg/kg body wt. The acetic acid-induced writhing method was found effective to evaluate peripherally active analgesics. The agent reducing the number of writhing will render analgesic effect preferably by inhibition of prostaglandin synthesis, a peripheral mechanism of pain inhibition.

Chronic Anti-Inflammatory Studies by Cotton Pellet Induced Granuloma

M E at the two doses used in the study inhibited granulomatous tissue. The amount of exudates produced in response to insertion of the cotton pellet was found to decrease dose-dependently on treatment with AW (200 mg/kg) extracts. The extract was potent in inhibiting both the exudative and proliferative phases of granuloma formation (table no.4).

Table No. 4: The Effect of *HAME*/Indomethacin on Granuloma Tissue of Cotton Pellet-Induced Granuloma in Rats

GROUPS	GRANULOMA TISSUE		PERCENTAGE INHIBITION	
	Wetwt.(mg)	**Drywt.(mg)**	**Wetwt.**	**Drywt.**
Control	0.335±0.07	0.075±0.013	—	—
Standard	0.218±0.02**	0.054±0.016**	34.92%	28%
HAME 200mg/kg	0.192±0.02**	0.047±0.016**	42.68%	37.33%
HAME 400mg/kg	0.142±0.01**	0.037±0.004**	57.6%	50.66%

Results were expressed as mean ± SEM, (n=5), One way ANOVA by Dunnet test comparison between control group. The data were considered significant if * $p<0.05$, **$p<0.001$.

Evaluation of Antipyretic Activity

Antipyretic Activity by Yeast Induced Hyperthermia Model

Antipyretic activity of HAME showed in (Table.no.5). The animals were treated with the standard drug Paracetamol 150mg/kg p.o. showed a significant decrease in rectal temperature of the body ($p<0.001$) when compared to control. A high dose of test drug HAME (400 mg/kg) showed a significant reduction in body temperature ($p<0.001$) from the 2nd hour onwards after drug administration. While the low dose of 200 mg/kg showed a significant reduction of the body temperature of the rat at 3rd h ($p<0.05$).

Table No. 5: Effect of Hydro-Alcohol Extract of *Mussaenda erythrophylla* on Yeast Induced Hyperthermia Model

GROUP	RECTAL TEMPERATURE IN ºCATTIME (HR)					
	Before Yeast injection	**0hr**	**1hr**	**2hr**	**3hr**	**4hr**
Control	37.00± 0.036*	38.20± 0.005*	38.89± 0.013*	39.55± 0.007*	40.00± 0.015*	40.40± 0.005*
Standard	37.01± 0.010*	38.00± 0.015*	37.56± 0.006*	37.45± 0.018*	37.36± 0.015*	37.10± 0.016*
HAME 200mg/kg	37.03± 0.022*	38.25± 0.025*	38.30± 0.010*	38.33± 0.057*	37.79± 0.002*	37.03± 0.010*
HAME 400mg/kg	37.02± 0.003*	38.10± 0.022*	38.15± 0.042*	37.56± 0.004*	37.50± 0.009*	37.40± 0.005*

Results were expressed as mean ± SEM, (n=5), One way ANOVA by Dunnet test comparison between control group. The data were considered significant if * $p<0.05$, ** $p<0.001$.

The effect of HAME on the rectal temperature in rats is presented in Table no. 5. The subcutaneous injection of yeast suspension markedly elevated the rectal temperature after 18h of administration. Treatment with HAME at a dose of 200, 400mg/kg decreased the rectal temperature of the rats in a dose-dependent manner. It was found that the extract at a dose of 200 mg/kg caused a significant lowering of body temperature at 4 hours following its administration (37.03 ± 0.010). This effect was maximal at a dose of 400mg/ kg and it caused a significant lowering of body temperature ($P< 0.01$) up to 4 hours after its administration (36.75± 0.005). The antipyretic effect started as early as 1h and the effect was maintained for 4h, after its administration. Both the standard drug Paracetamol 10mg/kg and tested drug HAME were significantly reduced the yeast-elevated rectal temperature, at 2^{nd}, 3^{rd} and 4^{th} hour compared to the control group.

CONCLUSION

Mussaenda erythrophylla is used for Analgesic, Anti-inflammatory, Antipyretic activities. In the present study, an attempt was made to take an extract of ME, which does not cause any

side effects or adverse reactions. In the present investigation, the plant material was collected from in the local region of Calicut, Kerala, and was authenticated. Hydroalcoholic extract of *Mussaenda erythrophylla* was prepared by the maceration process after extraction preliminary phytochemical studies were carried out. The hydroalcoholic extract was found to possess saponins and flavonoids. So the anti-inflammatory activity of this plant may be the presence of this chemical constituent. Flavonoids are known to inhibit the enzyme prostaglandin synthesis, more specifically the endoperoxide, and are reported to produce anti-inflammatory effects and analgesics. The present results also showed that the HAME possessed a significant antipyretic effect in yeast-induced elevation of body temperature in experimental rats. Flavonoids are known to target prostaglandins which are involved in pyrexia. Hence the presence of flavonoids in the HAME may be contributory to its antipyretic activity. Acute toxicity studies were carried out according to OECD 425 guidelines and two doses were selected (200 and 400 mg). The extract at both doses 200 mg/kg and 400 mg /kg body weight shows significant analgesic activity in Hot plate method, Acetic acid-induced writhing method models by reducing paw edema volume when compared with control. The high dose (400 mg) showed more activity than the low dose (200 mg). The extract at both doses 250 mg/kg and 500 mg /kg body weight shows significant anti-inflammatory activity in Carrageenan induced paw edema and cotton pellet induced granuloma models by reducing paw edema volume when compared with control. The high dose (400 mg) showed more activity than the low dose (200 mg). HAME shows significant antipyretic activity. Brewer's yeast pyrexia models showed a significant reduction in body temperature as compared to control. 200mg is not sufficient but 400mg produces activity similar to that of standard drug Paracetamol 150mg/kg. To summarize the present work, we would like to state that HA extract of *Mussaenda erythrophylla* was found to be a potent analgesic, anti-inflammatory, antipyretic activity. Following the present study, it has been observed that *Mussaenda erythrophylla* has marked beneficial effects against centrally, peripherally, and inflammatory pain models. This protective action may be attributed to the presence of flavonoids and sterols. We would like to conclude that it is worthwhile to think, to use *Mussaenda erythrophylla* as a drug and further studies should be initiated to establish the exact mechanism of action and elaborative phytochemical investigations to find out which active constituents are responsible for analgesic, anti-inflammatory, antipyretic activity. These reports may serve as a footstep in the research of potent analgesic, anti-inflammatory, antipyretic drugs.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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