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INVESTIGATION OF ANALGESIC AND ANTI-INFLAMMATORY ACTIVITY OF MUSA PARADISIACA ROOTS

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ABSTRACT

Narcotics and non -narcotics are used in the management of pain and inflammation, both of which have side effects, thereby emphasizing the search for natural substances. The present study is to evaluate the Anti-inflammatory and analgesic activity of *Musa paradisiaca.* Albino Wistar rats of either sex weighing 180-200 g were used. Carrageenan induced paw edema and Egg-albumin induced paw edema models were used to evaluate the anti-inflammatory activity and Formalin induced paw licking test, Tail immersion test, and Acetic acid-induced writhing test was used to evaluate analgesic models. Ethanolic Extract of *Musa Paradisiaca* showed a significant decrease in paw volume in both carrageenan-induced inflammation and egg-albumin-induced inflammation. In Formalin induced paw licking test and Tail immersion test, it showed marked depletion in pain, and in the acetic acid-induced writhing test it showed a significant decrease in the number of writhes compared to the positive control group. EEMP exhibits significant anti-inflammatory and analgesic effects throughout the activity.

KEYWORDS: Anti-inflammatory, Analgesic, Indomethacin, Diclofenac sodium, *Musa paradisiaca.*

INTRODUCTION

Inflammation or phlogosis could also be a pathophysiological response of living tissues to injuries that leads to the local accumulation of plasmatic fluid and blood cells. Although it is a defense reaction, the complex events and mediators involved in the inflammatory reaction can induce, maintain or aggravate many diseases. Therefore, the utilization of anti-inflammatory agents is useful within the treatment of that pathologies.[1]

Acute inflammation is that the immediate and early response to injury designed to deliver leukocytes to sites of injury. Once there, leukocytes clear any invading microbes and start the method of breaking down necrotic tissues.[2] Chronic inflammation can be considered to be inflammation of prolonged duration (weeks to months to years) in which active inflammation, tissue injury, and healing proceeds simultaneously.[3]

Chronic inflammation may result from failure of the recovery phase of acute inflammation or may occur as a distinct process from the outset, because of the nature of the irritant. It may be divided into non-granulomatous and granulomatous chronic inflammation; the term granuloma refers to a localized collection of activated macrophages and their derivatives. In granulomatous inflammation, T cell-derived cytokines promote the formation of multinucleated giant cells by the fusion of macrophages.[4]

Musa paradisiaca L is an herbaceous plant (up to 9 m long) with a robust tree-like pseudo-stem, a crown of large elongated oval deep-green leaves (up to 365 cm in length and 61 cm in width), with a prominent midrib, each plant produces one inflorescence like drooping spike, and ovate, 15-20 cm long, concave, dark red and somewhat fleshy.[5] The Phytochemical screening of extract revealed the presence of various constituents such as Carbohydrates, flavonoids, saponins, tannins, glycosides, steroids.[6] Studies have also shown that it has antiulcerogenic, antilithiatic, antimicrobial, antihypertensive, analgesic, wound healing, and vasodilatory activities.[7]

Despite such vast pharmacological benefits, the scientific evidence on the anti-inflammatory activity of *Musa paradisiaca* root is not clear. Hence it was planned to evaluate the effects of *Musa paradisiaca* root extract using suitable animal models.

MATERIAL AND METHODS

Ethics

Ethical clearance (Ref.No.01 SJMCP/IAEC/2019-20) for performing experiments on animals was obtained from Institutional Animal Ethical Committee (IAEC) Ref.No.02 SJMCP/IAEC/2020-21

Animals

Healthy young adult Wistar Albino Rats (150-200 g) of either sex, were used for the Screening of Anti-inflammatory and Analgesic activity. The rats were grouped in separate

cages with six animals in each cage, and the floor was covered with husk. They were housed in an animal house at a temperature of 23ºC ± 2ºC, the humidity was maintained for 40%-70%, acclimatized for 3 days. The animals were fed standard pellet food and given tap water *ad libitum.*

Preparation of plant extract

The roots were dried separately at room temperature and pulverized. The powder obtained is subjected to Soxhlet extraction with the ethanol solvent. Then it is used for biological investigations and after subjecting it to preliminary qualitative Phytochemical studies. The extracts were concentrated under reduced pressure and stored in a Refrigerator less than 10^0c until further use and the percentage yield of corresponding extracts was calculated. The stock solutions of ethanolic extracts were prepared using 1% CMC and used for oral administration to animals.

Experimental design

For each of the experiments, 30 animals were randomized into five groups (Negative, Positive, Standard, Low dose, High dose) of six animals each. The animals in negative control received Normal saline in Orally and the animals in the Positive control group are served as the disease group. Indomethacin and Diclofenac sodium was administered as Standard drug orally in the standard group at a dose of 10mg/kg and 100mg/kg b.w respectively. The low dose and High dose groups received an ethanolic extract of *Musa paradisiaca* at a dose of 250mg/kg b.w and 500mg/kg b.w respectively.

Phytochemical screening of the extract

The phytochemical screening, as well as identification of the plant extract, was done by standard chemical methods

Evaluation of analgesic activity

A. Formalin-Induced paw licking test[8]

Group 1: Negative Control (Normal saline 10ml/kg).

Group 2: Positive Control Formalin (0.02ml/kg).

Group 3: Diclofenac sodium (100mg/kg) + Formalin (0.02ml/kg).

Group 4: Formalin + *Musa paradisiaca* extract (250mg/kg b.w p. o).

Group 5: Formalin + *Musa paradisiaca* extract (500mg/kg b.w p. o).

Procedure

Formalin-induced paw licking test was performed according to Hunskaar and Hole. Thirty rats will be selected for the experiment and divided into 5 groups. The Control group, Standard group, and test group were treated with distilled water (10mg/kg), diclofenac sodium (DS, 100mg/kg), and EEMP at 250 and 500 mg/kg, respectively. All of the treatment processes were done by oral gavage Moreover, 1h later of treatment, each rat was injected with 20µl of 2.7% (v/v) formalin solution into the dorsal surface of the left hind paw. Animals were observed for 5 min after injection, which was considered as acute phase. Again, they were monitored for 5 min after 20 min of injection which was defined as a late phase.

B. Tail Immersion test[9]

Group 1: Positive Control Dipping the tail in hot water (55º ± 1º C).

Group 2: Diclofenac sodium (100mg/kg).

Group 3: Formalin + *Musa paradisiaca* extract (250mg/kg b.w p. o).

Group 4: Formalin + *Musa paradisiaca* extract (500mg/kg b.w p. o).

Procedure

The central mechanism of pain or analgesic activity can be evaluated by the experiment. Thermal stimuli act as the generator of painful reaction through dipping the tail tip in hot water (55º ± 1º C). Rats were grouped and treated as described before. Diclofenac sodium (100mg/kg) was used as a standard drug. Basal reaction time was counted for each rat after one hour of treatment. The counting was after 30, 60, 90, and 120 min of the respective treatment to determine the latency period. Moreover, each group was also monitored for a latency period before 30min of treatment. The animal which had more than 15 s latency periods was removed from the experiment and 15s acts as a cut-off point to avoid injury.

C. Acetic acid induced writhing test[10]

Group 1: Negative Control (Normal saline 10ml/kg).

Group 2: Positive Control Acetic acid (10ml/kg).

Group 3: Diclofenac sodium (100mg/kg) + Acetic acid (10ml/kg).

Group 4: Acetic acid + *Musa paradisiaca* extract (250mg/kg b.w p. o).

Group 5: Acetic acid+ *Musa paradisiaca* extract (500mg/kg b.w p. o).

Procedure

Rats were kept unfed for 16 h with water *ad-libitum* before the experiment and pretreated

with extracts as mentioned before. Diclofenac sodium acted as standard control; meanwhile, distilled water acted as normal control. Each rat was injected intraperitoneally with 0.7% (v/v) acetic acid at a dose of 10ml/kg body weight after 45 min of respective treatment. Soon after acetic acid injection number of writhes was counted for thirty minutes. Meanwhile, after 45 min the number of writhing responses was recorded for each animal during a 5 min period. Then began after 15 min of acetic acid administration.

Evaluation of anti-inflammatory activity

D. Egg Albumin-Induced inflammation[11]

Group 1: Negative Control (Normal saline 10ml/kg).

Group 2: Positive Control Egg-Albumin (0.1ml/kg).

Group 3: Indomethacin (10mg/kg) + Egg-Albumin (0.1ml/kg).

Group 4: Egg-Albumin + *Musa paradisiaca* extract (250mg/kg b.w p. o).

Group 5: Egg-Albumin + *Musa paradisiaca* extract (500mg/kg b.w p. o).

Procedure

Inflammation was induced in rats by the injection of egg albumin (0.1ml, 20% in normal saline) into the sub planter tissue of the right hind paw. Test drugs were administered to 24 h fasted rats 1h before the induction of inflammation. The swelling degree of the injected paw was measured before and 0.5, 1, 2, 3, and 4 h after the administration of the phlogistic agent. Results were expressed as the increase in paw volume (in ml) calculated after subtraction of basal paw volume.

E. Effect of carrageenan-induced inflammation[12]

Group 1: Negative Control (Normal saline 10ml/kg).

Group 2: Positive Control carrageenan 1%

Group 3: Indomethacin (10mg/kg) + carrageenan 1%

Group 4: Carrageenan + *Musa paradisiaca* extract (250mg/kg b.w p. o).

Group 5: Carrageenan + *Musa paradisiaca* extract (500mg/kg b.w p. o).

Procedure

Healthy Wistar Albino rats of either sex will be taken for the experiment. Rats will be divided into 5 groups of 6 animals each. Displacement of the normal paw will be measured before treatment. The rats will receive physiological saline, Musa paradisiaca extract, and indomethacin respectively. At 60min after the last treatment, rats will be infected with 0.1

mL of carrageenan suspension (0.1g/mL) in the right hind paw. The volume change will be measured at 1, 2, 3, and 4 h by using a plethysmometer Later percentage inhibition will be calculated.

$$\text{Percentage inhibition} = \frac{(V1)_{\text{control}} - (V2)_{\text{treated group}} \times 100}{(V2)_{\text{control}}}$$

Statistical analysis

The data obtained from the above findings will be subjected to statistical analysis using one-way ANOVA followed by Tukey's Kramer Multiple Comparison Test to assess the statistical significance of the results.

RESULTS

Phytochemical screening test

A phytochemical test of *Musa paradisiaca* was performed and it was evaluated that the ethanolic extract of the plant shows the presence of the following phytoconstituents.

Sl. no.	Phytoconstituents	Alcohol extract
1.	Carbohydrates	+
2.	Proteins	+
3.	Tannins	+
4.	Saponins	+
5.	Triterpenoids	+
6.	Flavonoids	+
7.	Resins	-
8.	Glycosides	+
9.	Alkaloids	+
10.	Steroids	+
11.	Quinones	-

Table 1: Effect of EEMP on Formalin-Induced paw licking test.

Sl. no	Groups	% Inhibition Mean ± SEM	
		Early phase	Late Phase
I	Negative control	52.6 ± 0.66	39.0 ± 0.25
II	Positive control	81.16 ±0.60	53.0 ± 0.73
III	Standard (Diclofenac Sodium)	58.5 ± 0.49***	27.6 ± 0.42***
IV	Low dose (EEMP) 250mg/Kg	73.83 ± 2.41**	40.83 ± 2.30**
V	High dose (EEMP) 500mg/Kg	64.3 ± 1.99**	35.0 ± 2.80**

EEMP: Ethanolic extract of *Musa Paradisiaca L* represent Values are Mean ± S.E.M. (n=6); Significance values are: ***$P < 0.001$, **$P < 0.01$ and *$P < 0.05$. Positive group vs. all groups. (By one-way ANOVA followed by Tukey-Kramer multiple comparison tests).

1. **Evaluation of the Analgesic activity of alcoholic extract of *Musa Paradisiaca L* in Formalin-Induced Paw Licking Test**

The alcoholic extract of *Musa Paradisiaca L* was screened for Analgesic activity by Formalin-Induced Paw Licking Test using Wistar albino rats of either sex weighing 150-200 gm, the parameter studied in this model were Early-phase and late phase. The persistent-pain model of formalin-induced hind paw licking was used in the study. The first phase of pain is attributed to the direct activation of nociceptors and primary afferent fibers by formalin, causing the release of bradykinin and tachykinins. This phase is inhibited by opioid analgesics. The effects of EEMP on formalin-induced paw licking are depicted in Table. 1.

2. **Evaluation of the analgesic activity of alcoholic extract of *musa paradisiaca l* in tail immersion test**

Table 2: Effect of EEMP on tail immersion test.

Groups	Treatment	Mean Latency to Tail Immersion (Sec)			
		30 MIN	60 MIN	90 MIN	120 MIN
I	Control	3.6 ± 0.3	5.0 ± 0.36	4.0 ± 0.45	5.0 ± 0.36
II	Standard (Diclofenac Sodium)	9.0± 0.69***	10.8 ± 0.60***	9.1± 0.36***	8.3 ± 0.33***
III	Low dose (EEMP)250mg/Kg	3 ± 0.30**	7.5± 0.42**	8.0± 0.36**	7.5± 0.42**
IV	High dose (EEMP)500mg/Kg	8.0± 0.82**	9.5± 0.76**	8.5± 0.45**	7.8 ± 0.30***

Ethanolic Extract of *Musa Paradisiaca L* represent Values are Mean ± S.E.M. (n=6); Significance values are: ***$P < 0.001$, **$P < 0.01$ and *$P < 0.05$. Positive group vs. all groups. (By one-way ANOVA followed by Tukey-Kramer multiple comparison tests).

The tail immersion test is a thermal test for evaluating the analgesic potential of a compound. Several clinically approved pharmacological agents have been demonstrated to delay the onset of heat sensitivity upon tail exposure to heat including opioids such as morphine, alpha-adrenergic compounds. The effect of the EEMP on the Tail immersion test is analyzed in Table. 2.

3. Evaluation of the Analgesic activity of alcoholic extract of *Musa Paradisiaca L* in Acetic acid Induced writhing Test

Table 3: Effect of EEMP on Acetic Acid-Induced writhing test.

Sl. no.	Groups	% Inhibition	
		Mean ± SEM	
		Early Phase	Late Phase
I	Negative control	43.6 ± 0.76	18.0 ± 0.85
II	Positive control	56.8 ± 0.79	28.5 ± 0.92
III	Standard (Diclofenac Sodium)	29 ± 0.49***	11.1 ± 0.42***
IV	Low dose (EEMP)250mg/Kg	40.5 ± 1.86**	18.1 ± 1.37**
V	High dose (EEMP)500mg/Kg	36.6 ± 1.89**	14.3 ± 1.24**

Ethanolic extract of *Musa Paradisiaca L* represent Values are Mean ± S.E.M. (n=6); Significance values are: ***$P < 0.001$, **$P < 0.01$ and *$P < 0.05$. Positive group vs. all groups. (By one-way ANOVA followed by Tukey-Kramer multiple comparison tests).

When animals are intraperitoneally injected with acetic acid, a painful reaction and acute inflammation emerge in the peritoneal area. Constriction induced by acetic acid is considered to be a nonselective antinociceptive model, as acetic acid acts indirectly by inducing the release of endogenous mediators which stimulate the nociceptive neurons that are sensitive to nonsteroidal anti-inflammatory drugs to narcotics, and other centrally active drugs. The effect of EEMP on the Acetic Acid induced writing test is presented in Table. 3.

4. Evaluation of Anti-inflammatory activity of alcoholic extract of *Musa Paradisiaca L* in Egg Albumin-Induced Inflammation

Table 4: Effect of EEMP on Egg Albumin-Induced inflammation.

Groups	Treatment	Percentage Of Inhibition			
		1 Hour	2 Hour	3 Hour	4 Hour
I	Negative control	33.3± 0.66	33.3 ± 1.20	33.8 ± 0.60	34.1 ± 1.19
II	Positive control	61.3 ± 0.71	64.0 ± 0.57	66.5 ± 0.56	59.0 ± 0.67
III	Standard (Indomethacin)	55.3± 0.8 ***	59.5± 0.42***	61.3± 0.61***	53.5± 0.67***
IV	Low dose (EEMP)250mg/Kg	49.6± 1.62**	52.1± 1.06**	57.3± 1.25**	48.1± 1.22***
V	High dose (EEMP)500mg/Kg	52.3± 1.30**	55.2± 2.08*	59.83± 1.47*	52.3± 1.54*

Ethanolic extract of *Musa Paradisiaca L* represent Values are Mean ± S.E.M. (n=6); Significance values are: ***$P < 0.001$, **$P < 0.01$ and *$P < 0.05$ Positive group vs. all group. (By one -way ANOVA followed by Tukey-Kramer Multiple comparison tests).

In normal rats, EEMP (250 & 500mg/kg) treatment showed a significant inhibitory effect on rat paw edema development in the middle phase and more pronouncedly in the later phase of the egg albumin-induced inflammation. Moreover, histamine may induce paw edema in rats by evoking the release of prostaglandin & inflammatory mediators. The effect of EEMP on Egg albumin-induced inflammation is tabulated in Table. 4.

5. Evaluation of Anti-inflammatory activity of alcoholic extract of *Musa Paradisiaca L* in carrageenan-induced Inflammation

Table 5: Effect of EEMP on carrageenan Induced Inflammation.

Groups	Treatment	Percentage of Inhibition			
		1 Hour	2 Hour	3 Hour	4 Hour
I	Negative control	21.5 ± 0.42	21.0 ± 0.36	21.5 ± 0.42	21.5 ± 0.42
II	Positive control	34.8 ± 0.60	36.6 ± 0.33	37.3 ± 0.42	33.6 ± 0.49
III	Standard (Indomethacin)	30.1± 0.40***	32.1± 0.47***	33.1± 0.47***	29.6± 0.33***
IV	Low dose (EEMP)250mg/Kg	26.5± 1.33**	29.3± 0.88**	30.6± 0.88**	26.6± 1.42*
V	High dose (EEMP)500mg/Kg	27.3± 1.40*	31.5± 0.56***	31.8± 0.70***	27.3± 1.08**

Ethanolic extract of *Musa Paradisiaca L* represent Values are Mean ± S.E.M. (n=6); Significance values are: ****P* < 0.001, **P < 0.01 and *P < 0.05. Positive group vs. all groups. (By one-way ANOVA followed by Tukey-Kramer multiple comparison tests).

The significant paw edema inhibition of EEMP at all assessment times in this model was suggested that the mechanism of the anti-inflammatory effect of EEMP may partly involve the release or the synthesis of the predominant pro-inflammatory mediators synthesized and/or released during these periods i.e., COX pathway products. The effect of EEMP on Carrageenan-induced inflammation is given in Table No 5.

DISCUSSION

Many plants are essential in human health care, both in self-medication and in national health services. Ironically, many plants that save lives are themselves in need of saving, not from diseases but an ever-expanding human population whose growth and consumption of natural resources are threatening plant diversity in most parts of the planet.[13] Musa paradisiaca is an herbaceous plant (up to 9 m long) with a robust tree-like pseudo-stem, a crown of large elongated oval deep-green leaves (up to 365 cm in length and 61 cm in width), with a prominent midrib, each plant produces a single inflorescence like drooping spike, and large bracts opening in succession, ovate, 15-20 cm long, concave, dark red and somewhat fleshy.

Fruits are oblong, fleshy, 5-7cm long in wild form, and longer in the cultivated varieties. Musa sapientum is a tree-like perennial herb that grows 5 - 9 m in height, with tuberous rhizome, hard, long pseudostem. The inflorescence is big with a reddish-brown bract and is eaten as vegetables. The ripe fruits are sweet, juicy, and full of seeds and the peel is thicker than another banana.[14]

Our results show that EEMP has an inhibitory effect on the analgesic response in both the early and late phases of the formalin test. Moreover, significant pain relief activity observed in the late phase (compared to the early phase) indicates the peripherally acting protective effect of EEMP, which was correlated with anti-inflammatory tests results.[15] The result of the analgesic activity study of *Musa paradisiaca L* by tail Immersion method showed a significant ($p<0.01$) increase in pain threshold compared with the control, where the effect increased to a maximum at 60 minutes post the extract administration, and gradually decreased as the time increased from 60 minutes to 120 minutes following administration of the extract in all the doses used, including the standard drug (diclofenac).[16]

When animals are intraperitoneally injected with acetic acid, a painful reaction and acute inflammation emerge in the peritoneal area. Constriction induced by acetic acid is considered to be a nonselective antinociceptive model, as acetic acid acts indirectly by inducing the release of endogenous mediators which stimulate the nociceptive neurons that are sensitive to nonsteroidal anti-inflammatory drugs to narcotics, and other centrally active drugs.[17-19] In normal rats, EEMP (250 & 500mg/kg) treatment showed a significant inhibitory effect on rat paw edema development in the middle phase and more pronouncedly in the later phase of the egg albumin-induced inflammation. Moreover, histamine may induce paw edema in rats by evoking the release of prostaglandin & inflammatory mediators.[16-19] The significant paw edema inhibition of EEMP at all assessment times in this model was suggested that the mechanism of the anti-inflammatory effect of EEMP may partly involve the release or the synthesis of the predominant pro-inflammatory mediators synthesized and/or released during these periods i.e., COX pathway products.[20-23]

CONCLUSION

The oral administration of EEMP has shown a significant anti-inflammatory effect when compared to control. The anti-inflammatory effect has been proved with carrageenan-induced paw edema and egg albumin-induced inflammation. It can be concluded that active constituents are responsible for Anti-inflammatory and analgesic activity that might be

present in the extract of the roots. However, further studies are necessary to find the exact mechanism of Anti-inflammatory and analgesic activity and to isolate the active compound(s) responsible for this pharmacological activity. The result indicates and shown better Anti-inflammatory and analgesic activity in experimental Rat models, it is due to the presence of tannins, flavonoids, and other polyphenolic compounds. Hence, the research justifies that ethanolic extract of *Musa paradisiaca L* can be effectively used in the treatment of Anti-inflammatory and analgesic activity.

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