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"EVALUATION OF ANTI-INFLAMMATORY AND ANALGESIC ACTIVITY OF CRUDE EXTRACT OF LEAVES OF *ASCLEPIAS CURASSAVICA* L"

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Abstract:

The present research work was aimed to investigate anti-inflammatory and analgesic activity of ethanolic extract of Asclepias curassavica L (EEAC) against Formalin Induced Paw licking, Tail Immersion test, Acetic acid writhing model, carrageenan-induced paw edema method, Egg Albumin-Induced Inflammation EEAC showed significant inhibition in the early phase compared to a late phase in Formalin Induced Paw licking and in Tail Immersion test EEAC at 500mg/kg produced highly significant and greater analgesic activity and in Acetic acid writhing model EEAC at dose 500mg/kg has shown significant reduction in several writing's. In the carrageenan-induced paw edema method, EEAC produced a significant reduction in paw volume in the 4th hour, and in Egg albumin-induced inflammation showed significant inhibition in paw volume in the 4th hour respectively. The mean reaction time, percentage of early and late phases, and the number of writhing were measured. The paw volume was measured using a Digital plethysmometer well as Egg Albumin-Induced Inflammation. However, the present study did not include the tests for establishing the extract mechanism of action.

Keywords: *Asclepias curassavica L; Anti-inflammatory; Analgesic; Carrageenan; Indomethacin.*

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INTRODUCTION:

Herbs and its extracts have been employed for healing purposes since the beginning of time, when stories, traditions, and literature were used to codify those plants that might relieve pain and treat ailments. The development of these herbal medicines, based primarily on local herbs, produced well-known traditional medicine systems, the Indian Ayurvedic and Unani, the Chinese and Tibetan from other parts of Asia, the North American of North America, the Amazonian of South America and various African local system.[1]

Understanding the relationship between medicinal plants in traditional medical systems can help to recognize plant materials with potential components for modern medicine.

Only 17 percent of the world's 250,000 species of higher plants have been formally studied for medical potential. [2] Plant diversity in terms of chemical and biological diversity is a potentially unlimited renewable resource for the development of novel medications.

Inflammation is the body's natural response to infection and injury. The inflammatory reaction has long been divided into various components, including redness, heat, discomfort, and edema.[3] Inflammatory injuries cause the production of a number of systemic mediators, such as cytokines and chemokines, which orchestrate cellular infiltration and, as a result, bring the inflammatory response to a halt and tissue integrity to be restored.

Chronic inflammation, on the other hand, can be caused by persistent inflammatory stimuli or a malfunction of the resolution phase's systems. Instead of being a reaction to illness, damage, or disease, chronic inflammation becomes a problem. [4] Due to its common occurrence; pain is a public health issue with substantial societal repercussions. Back pain is a sign of a number of illnesses, and it is believed that 80–100% of people will experience it at some point in their life. Anti-inflammatory medicines, such as analgesics, are used to treat pain and have analgesic effects at high doses. In this context, the suppression of nitric oxide (NO) and prostaglandin E2 has been proposed as a potential therapy for a range of inflammatory diseases. Despite the fact that there are several anti-inflammatory and analgesic medicines on the market, current pharmacological therapy is associated with adverse effects such as gastrointestinal irritation, bronchospasm and bleeding time extension. [5]

Studies using in vitro and in vivo models of inflammation have led to the discovery of a number of natural extracts with established anti-inflammatory properties over the last decade.[6] Despite the fact that its anti-inflammatory properties are well-documented, following up Phytochemical and pharmacological research were crucial in identifying and characterizing a number of natural active substances. In addition, the molecular pathways revealed in animal models are similar to those reported in human models. Their prospective clinical translation has also been aided by the models. [7]

Tropical milkweed *Asclepias curassavica* L is an erect, evergreen sub shrub in the Asclepiadoideae subfamily of the Apocynaceaeceae family. [8] The Asclepiadoideae subfamily has numerous medicinally significant plants, with about 250 genera and 3,000 species, 43 genera and 243 species of which are found in India. It has a woody stem with milky sap leaves that are decussate, lanceolate, tuberculous along nerves, and sharp at both ends, measuring 6-14 x 1-3.5 cm. Plant reaches a height of 1 m and has a diameter of 45-60 cm. Asclepiadoideae plants, in general, are a source of cytotoxicity and cardiac glycosides, as well as extremely useful prospective products for treating a variety of ailment. The main chemicals described in this family are glycosides (steroidal, pregnant), and flavonoids. [9] In this study, we attempt to investigate the potential anti-inflammatory and analgesic compounds that can be purified and used for pharmaceutical applications.

MATERIALS AND METHODS:

Plant material

The plant sample was identified and authenticated by botanist, Chitradurga, Karnataka. Then fresh mature leaves of *Asclepias curassavica* L were collected from the surrounding area, SJM College of Pharmacy, Chitradurga.

Preparation of plant extract

Freshly collected leaves were cleaned, shade dried at room temperature, coarse powdered and then extracted with ethanolic by Soxhlet extraction method. Thereafter, the extract was concentrated using rotary flash evaporator. The yield of the extract obtained was 10 %. The obtained crude extract was stored in airtight container in refrigerator below 10ºC for further studies.

The ethanolic extract of *Asclepias curassavica* L leaves was dissolved in distilled water and subjected to the following studies.

1. Preliminary Phytochemical screening.
2. Acute toxicity study.

3. Anti-inflammatory and Analgesic activity.

Preliminary Phytochemical screening.
Preliminary Phytochemical screening was carried out on test extract for the detection of phytoconstituents by following literature reported methods.

Experimental animals
The albino rats of Wistar strain 150-200 g and albino mice 20-30 g of either sex was used in the experimentation. The animals were procured from Biogen Laboratory animal facility, Bangalore – 562107. After randomization into various groups, animals were acclimatized for period of 10 days under standard husbandry condition as follows, Room temperature: 27 ± 3º, Relative humidity: 65 ± 10%, 12 hr. light/ dark cycle.

All the animals were fed with rodent pellet diet and water ad libitum under strict hygienic condition. The Study protocol was approved from (IAEC) **Ref.No.02 SJMCP/IAEC/2020-21** before initiation of the experiment.

Acute toxicity studies (LD_{50})
The acute toxicity of ethanolic extract of *Asclepias curassavica* L leaves was determined as per OECD guideline no.423. It was observed that the extract was not lethal to the rats even at 2000mg/kg dose and LD_{50} is 2500mg/kg. Hence $1/10^{th}$ (250 mg/kg) and $1/5^{th}$ (500 mg/kg) of LD_{50} cut-off values of the leaves extract were selected as screening doses for the Analgesic and Anti-inflammatory activity.

Evaluation of Analgesic and Anti-inflammatory activity.
A. Formalin-Induced Paw Licking Test [10]
Wistar albino rats of either sex weighing 150-250 g were selected and divided into five groups of 6 animals each**.**
Group I: 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 with *Asclepias curassavica* L extract (250mg/kg b.w. p. o).
Group 5: Formalin with *Asclepias curassavica* L extract (500mg/kg b.w. p. o).

Formalin-induced paw licking test was performed according to Hunskaar and Hole. Thirty rats were 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 EEAC at 250 and 500 mg/kg, respectively. All of the treatment processes were done by oral gavage Moreover, 1h later of treatment, and 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 [11]
Wistar albino rats of either sex weighing 150-250 g were selected and divided into five groups of 6 animals each.
Group I: Negative Control (Normal saline 10ml/kg).
Group 2: Positive Control Dipping the tail in hot water (55º ± 1º C).
Group 3: Diclofenac sodium (100mg/kg).
Group 4: *Asclepias curassavica* L extract (250mg/kg b.w. p. o).
Group 5: *Asclepias curassavica* L extract (500mg/kg b.w. p. o).

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 after30, 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 Writhing Test [12]
Wistar albino rats of either sex weighing 150-250 g were selected and divided into five groups of 6 animals each

Group I: 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 (10ml/kg) with *Asclepias curassavica* L extract (250mg/kg b.w. p. o).
Group 5: Acetic acid (10ml/kg) with *Asclepias curassavica* L extract (500mg/kg b.w. p. o).

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

D. Egg Albumin-Induced Inflammation [13]

Wistar albino rats of either sex weighing 150-250 g were selected and divided into five groups of 6 animals each

Group I: 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 with *Asclepias curassavica* L extract (250mg/kg b.w. p. o).
Group 5: Egg-Albumin with *Asclepias curassavica* L extract (500mg/kg b.w. p. o).

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 phlogiston 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 [14]

Wistar albino rats of either sex weighing 150-250 g were selected and divided into five groups of 6 animals each

Group I: Negative Control (Normal saline 10ml/kg).
Group 2: Positive Control carrageenan 1%
Group 3: Indomethacin (10mg/kg) carrageenan 1%
Group 4: carrageenan with *Asclepias curassavica* L extract (250mg/kg b.w. p. o).
Group 5: carrageenan with *Asclepias curassavica* L extract (500mg/kg b.w. p. o).

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, *Asclepias curassavica* L extract, and Indomethacin respectively. At 60min after the last treatment, rats will be infected with 0.1 mi 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.

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

Statistical analysis:

The data obtained from the above findings was 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:

Preliminary Phytochemical tests

A Phytochemical test of ***Asclepias curassavica* L** was performed and it was evaluated that the ethanolic extract of the plant shows several phytoconstituents like carbohydrates, Triterpenoids, flavonoids, tannins, saponins, phenolic compounds, Proteins, and Resins.

Phytoconstituents	Alcohol extract
Carbohydrates	+
Flavonoids	+
Tannins	+
Saponins	+
Triterpenoids	+

Formalin-Induced Paw Licking Test

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 EEAC on formalin induced paw licking are depicted in Table: 1.

Table 1: Formalin-Induced Paw Licking Test

Sl. No	Groups	% Inhibition	
		Mean ± SEM	
		Early phase	Late Phase
1	**Group I (Negative)**	52.6 ± 0.66	39.0 ± 0.25
2	**Group II (Positive)**	81.16 ± 0.60	53.0 ± 0.73
3	**Group III Diclofenac Sodium**	58.5 ± 2.29***	27.67 ± 1.58***
4	**Group IV (EEAC)250mg/kg**	75.0 ± 0.89***	40.67 ± 1.66**
5	**Group V (EEAC)500mg/kg**	68.83 ± 1.99**	36.83 ± 1.01***

EEAC: Ethanolic extract of *Asclepias Curassavica* L Bar 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)

Tail Immersion Test

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

Table 2: Tail Immersion test

Groups	Treatment	Mean Latency to Tail Immersion (Sec)			
		30 MIN M ± SEM	60 MIN M ± SEM	90 MIN M ± SEM	120 MIN M ± SEM
I	**Positive**	3.6 ± 0.3	5.0 ± 0.36	4.0 ± 0.45	5.0 ± 0.36
II	**Diclofenac Sodium**	9.0 ± 0.69***	10.8 ± 0.60***	9.0 ±0.36***	8.3 ± 0.30***
III	**(EEAC)250mg/Kg**	6.0 ± 0.57*	7.0 ± 0.36*	7.1 ± 0.79*	6.8 ± 0.30*
IV	**(EEAC)500mg/Kg**	7.8 ± 0.70**	8.3 ±0.61**	8.0 ± 0.44**	7.5 ± 0.42**

EEAC: Ethanolic Extract of *Asclepias Curassavica* L Bar 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).

Acetic acid writhing Test

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 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 to other centrally active drugs. The effect of EEAC on Acetic Acid induced writing test is Table: 3.

Table No 3: Acetic acid writhing Test

Sl. No	Groups	% Inhibition	
		Mean ± SEM	
		Early Phase	Late Phase
1	**Group I (Negative)**	43.66 ± 0.84	18.0 ± 0.85
2	**Group II (Positive)**	56.8 ± 0.79	28.5 ± 0.92
3	**Group III Diclofenac Sodium**	29.0 ± 2.81***	11.17 ± 1.27***
4	**Group IV (EEAC)250mg/kg**	40.5 ± 0.76***	15.50 ± 0.42***
5	**Group V (EEAC)500mg/kg**	34.3 ± 2.18***	13.67 ± 0.95**

EEAC: Ethanolic extract of *Asclepias Curassavica* L Bar 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).

Egg Albumin-Induced Inflammation.

In normal rats, EEAC (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 EEAC on Egg albumin-induced inflammation is tabulated in Table: 4.

Table 4: Egg Albumin-Induced Inflammation

Groups	Treatment	Percentage Of Inhibition			
		1 Hour	2 Hour	3 Hour	4 Hour
I	**Negative**	33.3 ± 0.66	33.3 ± 1.20	33.8 ± 0.60	34.1 ± 1.19
II	**Positive**	61.3 ± 0.71	64.0 ± 0.57	66.5 ± 0.56	59.0 ± 0.57
III	**Indomethacin**	54.0 ± 0.89***	59.5 ± 0.42***	61.3 ±0.61***	53.5± 0.67***
IV	**(EEAC)250mg/kg**	52.6 ± 0.84***	55.0 ± 1.15**	58.6 ± 1.28**	51.83±1.01**
V	**(EEAC)500mg/kg**	53.5 ± 1.11**	56.16 ± 1.35**	59.5 ± 0.99**	53.16 ± .94**

EEAC: Ethanolic extract of *Asclepias Curassavica* L Bar 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).

Carrageenan Induced Inflammation

The significant paw edema inhibition of EEAC at all assessment times in this model was suggested that the mechanism of the anti-inflammatory effect of EEAC 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 EEAC on Carrageenan-induced inflammation is given in Table: 5.

Table 5: Carrageenan Induced Inflammation

Groups	Treatment	Percentage Of Inhibition			
		1 Hour	2 Hour	3 Hour	4 Hour
I	**Negative**	21.5 ± 0.42	21.0 ± 0.36	21.5 ± 0.42	21.5 ± 0.42
II	**Positive**	34.8 ± 0.60	36.6 ± 0.33	37.3 ± 0.42	33.6 ± 0.49
III	**Indomethacin**	30.16 ± 0.40***	32.16 ± .47***	33.1 ± 0.47***	29.6 ± 0.33***
IV	**(EEAC)250mg/kg**	27.8 ± 1.32*	28.1± 1.40**	29.5 ± 1.40*	26.0 ± 1.48*
V	**(EEAC)500mg/kg**	29.3 ± 0.84**	31.5 ± 0.99*	32.3 ± 0.80**	27.3 ± 0.88**

Ethanolic extract of *Asclepias Curassavica L* Bar 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).

DISCUSSION:

The present study has been designed to elucidate the Analgesic and Anti-inflammatory activity of leaves of *Asclepias Curassavica* L on rats. The findings of results revealed that the extract has been shown significant Analgesic and Anti-inflammatory activity.

Thus, from the result of the current investigation, it may be inferred that the leaf extract of *Asclepias Curassavica* L possesses Analgesic and Anti-inflammatory activity. Further study regarding isolation and characterization of active principle responsible for the pharmacological activity is needed.

The early phase (0 to 5 min) reflects centrally mediated pain, which was a result of direct stimulation of nociceptors and is believed to be a non-inflammatory pain. The late phase (15 to 30min) persistent period is caused by local tissue inflammation. Experimental results demonstrated that substance P and bradykinin participate in the early

phase, while histamine, serotonin, prostaglandins, nitric oxide, and bradykinin are believed to be involved in the late phase of the formalin test response. [15]

The gradual decrease in pain thresholds as the time increased following the extract administration could be due to the effects of drug-metabolizing enzymes on the extract and the standard drug. The result of the study thus showed *Asclepias curassavica* L leaves is a potent analgesic source when compared with the increase in pain thresholds of the graded doses of the extract with the pain threshold of the standard drug (Diclofenac 100mg/kg) at different times following the extract administration. [16]

In acetic acid-induced abdominal writhes, arachidonic acid is released via the Cyclooxygenase pathway, and prostaglandin biosynthesis plays a role in the nociceptive mechanism. [17] *Asclepias curassavica* L extract showed a reduction in the number of writhes at the dose 250mg/kg (p.o) at 20mins time interval but not significant reduction at a higher dose. The abdominal constrictions produced after the administration of acetic acid are due to the sensitization of nociceptors to prostaglandins.

Egg albumin-induced edema results from the release of histamine and serotonin. In this study, EEAC showed a significant inhibitory effect on rat paw edema development in the middle phase and more pronouncedly in the later phase of egg albumin-induced inflammation. This suggests that EEAC possibly acts by inhibiting the release and/or actions of vasoactive substances (histamine, serotonin, and kinins) and prostaglandins. Moreover, histamine may induce paw edema in rats by evoking the release of prostaglandins and inflammatory mediators. [18]

The carrageenan injection involves three phases of inflammation that causes the paw edema: an initial phase (0-1.5 h) is attributed to the release of histamine and serotonin; a second phase (1.5-2.5 h) is attributed to the release of bradykinin; a third phase (2.5-4 h) is attributed to the synthesis of PGs (Pan Thong *et al*.). The significant paw edema inhibition of EEAC at all assessment times in this model was suggested that the mechanism of the anti-inflammatory effect of EEAC 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.[19]

CONCLUSION:

Analgesic and Anti-inflammatory Activity of ethanolic extract of *Asclepias curassavica* L was carried out by using five models. In the present study, the test sample of leaves extract was exhibited more Analgesic and Anti- inflammatory Activity ($P< 0.001$) when compared to the Positive group It can be concluded that active constituents are responsible for Analgesic and Anti-inflammatory activity that might be present in the leaves extract. However, further studies are necessary to find the exact mechanism of Analgesic and Anti-inflammatory activity to isolate the active compound(s) responsible for this pharmacological activity. The result indicates and shows better Analgesic and Anti-inflammatory 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 *Asclepias curassavica* L leaves can be effectively used in the treatment of Analgesic and Anti-inflammatory activity.

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