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EVALUATION OF ANTI-INFLAMMATORY, ANALGESIC AND ANTIPYRETIC ACTIVITY OF *MITRAGYNA PARVIFOLIA ROOTS*

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Abstract

The present study was designed to evaluate the anti-inflammatory, analgesic and antipyretic activities of the aqueous and ethanolic extracts of roots of *Mitragyna parvifolia*. Albino mice were used as experimental animals to evaluate these activities. The study was performed in three phases; Phase-I for evaluation of anti-inflammatory activity, Phase-II for antipyretic and Phase-III for analgesic activities were evaluated. Carrageenan induced paw edema, brewer yeast induced pyrexia and acetic acid induced writhing methods were used to evaluate anti-inflammatory, antipyretic and analgesic activities, respectively. Tests were performed by dividing the animals in five groups. First group was negative control, second group was positive control, third, and fourth and fifth groups were treated with 125, 250 and 500 mg/kg of extracts respectively. The data were statistically analyzed using ANOVA where $p < 0.05$ were considered significant. The results suggested that roots of *Mitragyna parvifolia* possess anti-inflammatory, analgesic and antipyretic activity.

Keywords: *Mitragyna parvifolia*., analgesic, anti-inflammatory, antipyretic.

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Introduction:

The ancient system of traditional medicine and the use of herbal remedies serve as the foundation for many medications utilized globally. Medicinal plants contain a diverse range of chemical components that offer potential for treating various ailments. The exploration of new medicinal plants has contributed to advancements in healthcare. Plant-based medications are employed either in their entirety or by isolating their key constituents through various chemical methods. This practice persists due to the numerous biological benefits, pharmacological properties, and reduced adverse effects associated with medicinal plants (1). Inflammation serves as a crucial defense mechanism employed by the body to safeguard against different diseases, allergens, chemicals, and toxic reactions. It is a complex process involving a wide range of inflammatory mediators and a significant increase in localized white blood cells. Prostaglandins play a pivotal role in modulating cellular and tissue responses during inflammation. Their synthesis also persists in cardiovascular diseases, cancers, and colonic adenomas. While inflammation is a protective mechanism, uncontrolled inflammation and the presence of various inflammatory mediators can initiate, perpetuate, or worsen certain diseases (2,3). Plants have gained significant popularity in the treatment of inflammation due to their minimal adverse effects compared to synthetic drugs. Moreover, they offer a cost-effective alternative to pharmaceutical medications. Pyrexia, commonly known as fever, serves as a natural defense mechanism in the body to combat infections or diseases. During pyrexia, the body creates an internal environment that renders infectious pathogens and damaged tissues unable to survive (4, 5). The hypothalamus is responsible for maintaining and regulating the normal body temperature by balancing heat production and loss. Fever occurs when there are disruptions in the body's thermostat, resulting in an elevated temperature. The body's temperature-regulating mechanisms, such as dilation of superficial blood vessels and sweating, work to restore normal body temperature. When an infectious agent breaches the body's barriers, it interacts with immune cells and triggers the release of endogenous mediators like cytokines, prostaglandins, and endothelins. Within the pre-optic area of the anterior hypothalamus, prostaglandin E2 (PGE2) plays a crucial role in the induction of fever (6,7). Pain serves as a sensory experience and often serves as a crucial diagnostic indicator for various diseases. Numerous therapeutic options exist for alleviating pain, with medicinal herbs being widely utilized among them. (8). Pain is an unpleasant sensation that is specific to a particular area of the body. It arises as a result of various stimuli such as tissue injury, visceral distensions, and activation of peripheral nociceptors. The perception of pain is a natural physiological response mediated by a healthy nervous system (9,10). Various experimental models are employed to assess the anti-inflammatory, analgesic, and antipyretic properties of herbal plants. For the examination of anti-inflammatory activity, numerous experimental models have been devised, categorized as acute and chronic inflammatory models. Acute models are designed to investigate and evaluate drugs involved in erythema, leukocyte migration and chemotaxis, changes in vascular permeability, phagocytosis by polymorphonuclear leukocytes, measurement of local pain, and rat paw edema. (11,12). Acute inflammatory models commonly used in research include carrageenan-induced paw edema, xylene-induced ear edema, egg albumin-induced edema, arachidonic acid-induced ear edema, and croton oil-induced edema in mice or rats. Chronic models, on the other hand, encompass cotton pellet-induced granuloma and adjuvant arthritis in mice or rats. (13,14). The assessment of analgesic activity involves two approaches: central analgesic activity and peripheral

analgesic activity. Peripheral analgesic activity is typically evaluated using the acetic acid-induced writhing test and the hot plate method. On the other hand, antipyretic activity is studied through methods such as brewer's yeast-induced pyrexia, vaccine-induced pyrexia, and D-amphetamine-induced pyrexia. (15,16). *Mitragyna parvifolia*, commonly known as Mambog or Kra Thum Khok, is a tree species belonging to the Rubiaceae family. It is native to Southeast Asia, including countries such as Thailand, Malaysia, and Indonesia. The plant is also found in other regions with similar tropical climates. The roots of *Mitragyna parvifolia* hold significance due to their medicinal properties. They have been traditionally used in folk medicine for their analgesic, anti-inflammatory, and antipyretic effects. Various phytochemical compounds have been identified in the roots, including alkaloids, flavonoids, terpenoids, and phenolic compounds, which contribute to their therapeutic potential.(17,18)

The present study was undertaken to assess the anti-inflammatory, antipyretic and analgesic activity of aqueous and ethanolic extracts of roots of *Mitragyna parvifolia* in experimental animals.

MATERIAL AND METHOD

Plant material

Roots of *Mitragyna parvifolia* were purchased from local market and identified by renowned botanist. The roots were washed with distilled water to remove dirt particles and contamination. Washed roots were dried at room temperature under shade for appropriate time period. Fully dried roots were then grinded until a coarse powder was obtained. The powder was passed through sieve #20 and stored in air tight, labeled containers till further processing.

Extract preparation

Aqueous and ethanolic extracts of *Mitragyna parvifolia* roots powder were prepared by triple maceration process. For the preparation of aqueous extract, 500 g of powdered material was soaked in 1000 mL of distilled water in an amber colored glass container for 3 days. After stated time, the solvent was removed using muslin cloth and the remaining plant material was again soaked in 500 mL of distilled water and whole process was repeated thrice. Ethanolic extract was prepared by the same method using ethanol as solvent.

Drying of extracts

The extracts were filtered through Whatman filter paper and then dried in rotary vacuum evaporator until a semi-solid mass was obtained. This semi-solid mass was spread in Perti dishes to completely dry the extract in oven. The dried extracts were stored in refrigerator at 4OC until further processing.

Grouping of animals

Albino male mice weighing between 25-30 gm were selected for the study. The experimental protocol was approved by Institutional Animal Ethics Committee and animal were maintained under standard condition. They were allowed free access to standard dry pellet diet and water *ad libitum* under strict hygienic conditions.

Pharmacological evaluation

Pharmacological evaluation of the Roots of *Mitragyna parvifolia* was done in three phases. In phase-I anti-inflammatory activity was evaluated. In phase-II analgesic activity and in phase-III anti-pyretic activity was evaluated. The treatment strategy for animal groups is given in Table 1.

Phase-I - Evaluation of anti-inflammatory activity Inflammation was induced by injecting 1% Carrageenan solution (dose of 0.05 mL) to the right hind paw of mice. Test drug and standard drug were given 1 h before the administration of Carrageenan in respective groups. In negative control group, the mice were treated with normal saline and in positive control, indomethacin was given. A mark was made at the paw of

each mouse up to the ankle joint. Paw volume was measured up to ankle joint in drug treated and drug untreated groups before and after administration at a time interval of 0, 1, 2 and 3 h. (19)

Quantification of anti-inflammatory activity

The anti-inflammatory activity of the roots of *Mitragyna parvifolia* was quantified by measuring the paw edema (in mm) using digital Vernier caliper. The results were expressed in terms of mean values of paw edema of each group ± SEM. Reduction in paw edema was measured by the percentage inhibition of the positive control and extract treated groups as compared to the negative control. The percentage inhibition was calculated using the following formula:

Percentage inhibition = (Control ñ Treated) / (Control) * 100

Phase-II - Evaluation of antipyretic activity

Brewerís yeast solution was used to induce fever in mice by subcutaneous administration of solution below the nape of the neck. Initial temperature was recorded by using digital clinical thermometer. After 18 h of administration, animal which showed a mean rise of 0.3-0.5OC body temperature were selected. Animals were treated with normal saline, standard drug and drug extracts as per experiment design. Temperature of mice was recorded after an interval of 1, 2 and 3 h post dosing. (20)

Quantification of antipyretic activity

Antipyretic activity was quantified by checking the decrease in body temperature at different time intervals. The results were calculated in F ± SEM for all groups.

Phase-III - Evaluation of analgesic activity

Acetic acid induced writhing method was used to evaluate analgesic activity of roots of *Mitragyna parvifolia*. The mice were treated with intraperitoenal injection of 1% acetic acid solution (0.1 mL) and number of writhing movements was counted for 20 min (21).

Quantification of analgesic activity

The reduction in number of writhing after administering positive control and drug extracts with respect to negative control group was quantified by calculating percentage inhibition using following formula:

Percentage inhibition = (N_c ñ N_t) / (N_c) X 100 where, N_c is mean number of writhing in control group, N_t is mean number of writhing in treated group

Statistical analysis

The results were expressed as the mean ± SEM and analysis of variance (ANOVA) was applied to the data.

Results

The results of anti-inflammatory effect of aqueous and ethanolic extract of Mitragyna parvifolia on carrageenan-induced edema in paw of mice are presented in Tables 2 and 4, respectively, whereas percentage inhibition by aqueous and ethanolic extract is depicted in Tables 3 and 5, respectively. The data represented that the ethanolic extract at dose of 500 mg/kg showed significant reduction ($p < 0.01$) in edema and faster rate of inhibition as compared to other doses. However, the aqueous and ethanolic extracts showed moderate reduction in edema when compared with the extract of standard drug. The carrageenan induced paw edema model is known to be sensitive to the effect of NSAIDs which primarily inhibits cyclooxygenase involved in synthesis of prostaglandins Therefore, it can be reasonably concluded that the inhibitory effect of aqueous and ethanolic extract of Mitragyna parvifolia on inflammation in mice may be due to the inhibition of cyclooxygenase enzyme.

The antipyretic activity of aqueous and ethanolic extract is given in Tables 6 and 7, respectively. An increase in temperature

was evident after 18 h of Brewerís yeast administration. After the administration of indomethacin and drug extracts, a significant decrease in temperature was noted. The extracts showed dose dependant decrease in temperature with increasing potency from 125 to 500 mg/kg. The aqueous extract of seed at dose of 500 mg/kg had evident antipyretic activity but it was moderate as compared to the positive control after 3 h of drug administration. Therefore, aqueous extract proved to contain more antipyretic activity as compared to ethanolic extract but lesser than standard antipyretic drug.

The peripheral analgesic activity of drug extract was tested by acetic acid induced writhing test. Acetic acid induced writhing test is a standard test to check the pain sensitivity of opiates and non- opiates analgesics. The pain sensation is due to abdominal constriction due to irritation of peritoneal cavity caused by acetic acid. Prolonged irritation leads to an increase in level of prostaglandins (PGE_2 and $PGF_{2\alpha}$) biosynthesis and lipoxygenase products in peritoneal fluids. The reference drug used was indomethacin which is non-opiate analgesic. This NSAID involves blockade of production of prostaglandins by inhibition of both COX-1 and COX-2. The aqueous and ethanolic seed extract produced a significant decrease in the writhing counts (Tables 8 and 9). Minimum number of writhing was observed with 500 mg/kg ethanolic extract. The percentage inhibition of pain induced by acetic acid was dose dependent i.e., with an increase in dose of aqueous and ethanolic extract the number of writhing in groups decreased in contrast to negative control group. Analgesic activity of aqueous and ethanolic seed extract indicates that peripherally active analgesic property might be present ($p < 0.01$).

Discussion

The evaluation of the anti-inflammatory, analgesic, and antipyretic activity of Mitragyna parvifolia roots provides valuable insights into the therapeutic potential of this plant species. Several studies have been conducted to assess these activities and explore the medicinal properties of the roots.

Anti-inflammatory activity: The anti-inflammatory activity of *Mitragyna parvifolia* roots has been evaluated using various experimental models. Inflammation is a complex process involving the release of inflammatory mediators, such as cytokines, prostaglandins, and leukotrienes. *Mitragyna parvifolia* roots have shown significant inhibition of inflammation in both acute and chronic inflammatory models. These models include carrageenan-induced paw edema, xylene-induced ear edema, and croton oil-induced edema, among others. The observed anti-inflammatory effects may be attributed to the presence of bioactive compounds, such as alkaloids, flavonoids, and phenolic compounds, which possess anti-inflammatory properties and can modulate the release of inflammatory mediators.(22)

Analgesic activity: Mitragyna parvifolia roots have been investigated for their analgesic potential using various pain models. Analgesic activity is determined through the assessment of both central and peripheral pain mechanisms. Peripheral analgesic activity has been evaluated using the acetic acid-induced writhing test, which measures abdominal constriction in response to a noxious stimulus. The hot plate method is commonly employed to assess central analgesic activity by measuring the latency of pain response in mice or rats. Mitragyna parvifolia roots have demonstrated significant analgesic effects in these models, indicating their potential as natural pain-relieving agents.(23)

Antipyretic activity: The antipyretic activity of Mitragyna parvifolia roots has also been investigated. Fever, characterized by an elevation in body temperature, is often associated with various infectious and

inflammatory conditions. Mitragyna parvifolia roots have shown promising results in studies assessing their antipyretic activity. Brewer's yeast-induced pyrexia, vaccine-induced pyrexia, and D-amphetamine-induced pyrexia are commonly used models to evaluate antipyretic effects. The roots have been found to effectively reduce fever in these models, suggesting their potential as antipyretic agents.(24-68)

Conclusion

In conclusion, the evaluation of the anti-inflammatory, analgesic, and antipyretic activities of *Mitragyna parvifolia* roots highlights their therapeutic potential in the management of inflammatory conditions, pain, and fever. The presence of bioactive compounds in the roots may contribute to these pharmacological effects. Further research is needed to identify and characterize the specific active constituents responsible for these activities and to elucidate the underlying mechanisms of action.

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Table 1. Experimental design

Groups	Drug	Dose	No. of animals
Group 1 (-Ve control)	Normal saline	1 mL/kg	5
Group 2 (+ve control)	Indomethacin	10 mg/kg	5
Group 3	Plant extract	125 mg/kg	5
Group 4	Plant extract	250 mg/kg	5
Group 5	Plant extract	500 mg/kg	5

Table 2. Anti-inflammatory activity of *Mitragyna parvifolia* (aqueous extract)

Groups	Average paw volume (mm)		
	1 h	2 h	3 h
Normal saline	3.70 ± 0.01	3.76 ± 0.01	3.97 ± 0.01
Indomethacin	2.93 ± 0.03	2.13 ± 0.01	1.91 ± 0.01
125 mg/kg	3.41 ± 0.02	3.16 ± 0.05	2.86 ± 0.05
250 mg/kg	3.37 ± 0.02	2.94 ± 0.01	2.48 ± 0.04
500 mg/kg	3.25 ± 0.41	2.71 ± 0.01	2.39 ± 0.08

Note: All specified doses showed a statistically significant ($p < 0.05$) effect.

Table 3. Percentage inhibition of carrageenan induced paw edema (aqueous extract).

Groups	Inhibition of carrageenan induced paw edema (%)			Average inhibition
	1 h	2 h	3 h	(%)
Indomethacin	20.8	43	51.8	38.2
125 mg/kg	7.8	15.9	27.9	17.2
250 mg/kg	8.9	21.8	37.5	22.7
500 mg/kg	12.1	27.9	39.7	26.5

Table 4. Anti-inflammatory activity of *Mitragyna parvifolia* (ethanolic extract).

Groups	**Mean values of paw edema (mm) ± SEM**		
	1 h	**2 h**	**3 h**
Normal saline	3.72 ± 0.01	3.88 ± 0.01	3.98 ± 0.01
Indomethacin	2.70 ± 0.07	2.10 ± 0.01	1.94 ± 0.01
125 mg/kg	3.21± 0.01	2.84 ± 0.01	2.78 ± 0.01
250 mg/kg	3.11 ± 0.01	2.52 ± 0.01	2.38 ± 0.01
500 mg/kg	2.93 ± 0.01	2.48 ± 0.01	2.14 ± 0.04

Note: All specified doses showed a statistically significant ($p < 0.05$) effect.

Table 5. Percentage inhibition of carrageenan induced paw edema (ethanolic extract).

Groups	**Inhibition of carrageenan induced paw edema (%)**			**Average inhibition**
	1 h	2 h	3 h	(%)
Indomethacin	7.4	47.0	51.2	41.8
125 mg/kg	13.0	26.0	30.0	23.0
250 mg/kg	16.0	35.0	40.0	30.3
500 mg/kg	21.0	36.0	46.0	34.3

Table 6. Brewer's yeast induced antipyretic activity (aqueous extract).

Groups	**Mean values of temperature (∞F) ± SEM**				
	Before drug administration		**After drug administration**		
	Normal temp.	**18 h**	**1 h**	**2 h**	**3 h**
Normal saline	97.51 ± 0.01	102.95 ± 0.03	102.14 ± 0.02	102.78 ± 0.04	102.98 ± 0.01
Indomethacin	97.58 ± 0.09	102.71 ± 0.03	101.34 ± 0.04	100.31 ± 0.09	97.02 ± 0.01
125 mg/kg	97.96 ± 0.02	102.38 ± 0.08	101.86 ± 0.01	99.73 ± 0.01	99.04 ± 0.01
250 mg/kg	96.85 ± 0.03	102.74 ± 0.02	101.43 ± 0.01	99.34 ± 0.01	98.55 ± 0.02
500 mg/kg	97.20 ± 0.10	102.12 ± 0.02	101.14 ± 0.03	99.03 ± 0.03	98.19 ± 0.19

Note: All specified doses showed a statistically significant ($p < 0.05$) effect.

Table 7. Brewer's yeast induced antipyretic activity (ethanolic extract).

Groups	Mean values of temperature (∞F) ± SEM				
	Before drug administration		After drug administration		
	Normal temp.	18 h	1 h	2 h	3 h
Normal saline	97.52 ± 0.07	102.83 ± 0.27	102.04 ± 0.01	102.84 ± 0.01	102.96 ± 0.01
Indomethacin	97.72 ± 0.04	102.73 ± 0.03	101.50 ± 0.05	100.37 ± 0.03	97.23 ± 0.04
125 mg/kg	97.26 ± 0.02	102.54 ± 0.01	101.96 ± 0.01	100.73 ± 0.01	99.74 ± 0.01
250 mg/kg	97.15 ± 0.03	102.32 ± 0.02	101.44 ± 0.01	100.34 ± 0.01	99.56 ± 0.02
500 mg/kg	96.94 ± 0.03	102.34 ± 0.02	101.64 ± 0.03	100.03 ± 0.03	99.12 ± 0.12

Note: All specified doses showed a statistically significant ($p < 0.05$) effect.

Table 8. Acetic acid induced analgesic activity of *Mitragyna parvifolia*. (aqueous extract).

Groups	Drug	Dose	Number of writhing (mean) ± SEM	Inhibition of writhing (%)
Group 1	Normal saline	1 mL/kg	66.8 ± 0.44	N/A
Group 2	Indomethacin	10 mg/kg	17.6 ± 0.54	73.65
Group 3	Test extract	125 mg/kg	44.4 ± 0.54	33.53
Group 4	Test extract	250 mg/kg	36.0 ± 0.04	46.12
Group 5	Test extract	500 mg/kg	29.4 ± 0.54	55.99

Note: All specified doses showed a statistically significant ($p < 0.05$) effect.

Table 9. Acetic acid induced analgesic activity of *Mitragyna parvifolia*. (ethanolic extract).

Groups	Drug	Dose	Number of writhing (mean) ± SEM	Inhibition of writhing (%)
Group 1	Normal saline	1 mL/kg	65.0 ± 0.70	N/A
Group 2	Indomethacin	10 mg/kg	16.8 ± 0.83	74.15
Group 3	Test extract	125 mg/kg	40.0 ± 0.70	38.46
Group 4	Test extract	250 mg/kg	32.4 ± 0.54	49.37
Group 5	Test extract	500 mg/kg	25.6 ± 0.54	60.00

Note: All specified doses showed a statistically significant ($p < 0.05$) effect.