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Research Article

Evaluation of Analgesic Activity of the Siddha Polyherbal Formulation *Ettikottai Mathirai* Using Eddy's Hot Plate Method in Mice

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ABSTRACT

Background: Pain is a common and distressing experience that often leads individuals to seek medical help. While conventional analgesics such as opioids and NSAIDs are widely used, they are not without side effects and limitations. Traditional medicine systems like Siddha offer alternative approaches that may be both effective and safer. *Ettikottai Mathirai* (EM) is a classical Siddha polyherbal formulation traditionally used to manage pain and inflammation, especially in conditions categorized under Vaatha diseases. **Objectives:** This study aimed to evaluate the analgesic potential of EM using the Eddy's Hot Plate method in Swiss albino mice. **Materials and Methods:** The experiment included a vehicle control group, a standard group receiving Pentazocine (5 mg/kg), and two test groups receiving low (8.5 mg/kg) and high (17 mg/kg) doses of EM. The latency time to thermal stimulus was measured at multiple intervals post-treatment. **Results:** Results showed a dose-dependent increase in reaction time in EM-treated groups, with the high-dose group displaying effects comparable to the standard drug. **Conclusion:** These findings suggest that EM may act through central pain pathways, possibly enhanced by the synergistic effects of its herbal ingredients known as anti-inflammatory and analgesic properties. The study supports the traditional use of EM and highlights its potential as a promising alternative for pain relief. Further research, including clinical trials, is recommended to confirm its therapeutic value and safety in human populations.

Keywords: *Ettikottai Mathirai*, Analgesic Activity, Siddha Polyherbal Formulation, Internal Medicine, Eddy's Hot Plate Method.

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INTRODUCTION

Pain is a complex and subjective sensation that may or may not be linked to actual tissue damage. It can manifest in a variety of forms, such as sharp, pricking, shooting, dull, stabbing, or electrical-like sensations.[1,2] Though it serves as a critical protective mechanism, signaling potential harm to the body, pain often leads to significant discomfort and distress, which can become debilitating if unmanaged. It is one of the most frequently reported complaints in clinical settings, prompting individuals to seek medical attention.

Analgesic agents are employed to relieve pain symptoms without necessarily addressing the underlying cause. These drugs are particularly useful when the source of the pain cannot be immediately treated or removed. Analgesics are broadly classified into two main categories: opioids and non-opioid drugs, including Non-Steroidal Anti-Inflammatory Drugs (NSAIDs). NSAIDs are widely used in both acute and chronic pain management due to their ability to block prostaglandin synthesis by inhibiting the Cyclooxygenase (COX) enzyme.

The Siddha system of medicine, a prominent traditional healthcare system in South India, emphasizes holistic healing and disease prevention. According to Siddha philosophy, medicine is any substance that fortifies the body, aids in curing illness, and helps restore physiological balance. Siddha treatments are categorized into internal and external therapies, with *Mathirai* (pills) being a common internal remedy, known for its one-year shelf life.[3,4]

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Ettikottai Mathirai (EM) is a traditional polyherbal formulation referenced in the classical Siddha text *Naam Naadu Vaithiyam*. It is indicated for various types of pain, including those associated with conditions like *soolai* (abdominal or muscular pain), *iduppu vali* (sciatica), and other disorders associated with *Vaatham* (neuromuscular diseases).[5] The remedy is composed of four key herbal components and has gained a reputation among Siddha practitioners for its effectiveness in managing both pain and inflammatory disorders.

Exploring the pharmacological potential of such traditional remedies could offer promising therapeutic options, especially those that might be safer and more tolerable than conventional medicines. Merging ancient medical wisdom with modern scientific validation could result in innovative and effective strategies for pain management.[6] Despite its widespread use, there remains a lack of structured scientific evaluation for EM's analgesic properties. Hence, this study aims to assess the analgesic effects of *Ettikottai Mathirai* using a standardized experimental animal model.

MATERIALS AND METHODS

Choice of the test drug

The test drug "*Ettikottai Mathirai*" is one of the Polyherbal formulations for 18 types of soolai (Throbbing pain), Iduppu vali (Sciatica), Vaatham (related to joint disease) and Pungal (wound) which is indicated in the Siddha literature "Naam Nadu Vaithiyam" written by Veeraperumal Pillai.[5]

Ingredients of *Ettikottai Mathirai*

The components of EM are presented in Table 1.

Purification of Raw Drugs

i.Chukku-Soaked in limestone water for 3 hr dried, and the outer layer is peeled off,[7]
ii.Milagu-Soaked in sore buttermilk for 1 to 1 1/4 hr and then fried,[7]
iii.Kirampu- Bud of the flower was removed and then fired,[8]
iv.Ettikottai-Removed the outer skin and cotyledons of *Ettikottai* and deep fried it with ghee.[9]
Dosage: 65-130 mg/twice a day,

Adjuvant: Warm water or buttermilk,

Preparation of *Ettikottai Mathirai*

All the ingredients was roasted and made as a fine powder. Grind the powder gently by adding lemon juice until to make pills.[5]

Dosage: 65-130 mg/twice a day,

Adjuvant: Warm water or buttermilk.

Study Approval

The experimental protocol was approved by "The Institutional Animal Ethics Committee of the Centre for Laboratory Animal Technology and Research, Sathyabama Institute of Science and Technology, Sholinganallur, Chennai, Tamil Nadu-600119, India". IAEC approved no: SU/CLATR/IAEC/XXII/17/2024 dated 02.03.2024.

Evaluation of analgesic activity of *Ettikottai mathirai* in Swiss albino mice

Selection of Experimental Animals

Healthy Swiss albino mice (30 males), aged 6 to 8 weeks and weighing between 20-30 g, were obtained from the Centre for Laboratory Animal Technology and Research, Sathyabama Institute of Science and Technology, Sholinganallur, Chennai, Tamil Nadu-600119. Upon procurement, all animals underwent veterinary examination both at the time of purchase and at the end of the acclimatization period. They were acclimatized for 7 days prior to dosing and housed in polypropylene cages with corn husk bedding under controlled environmental conditions. The housing temperature was maintained between 24-28°C, with relative humidity ranging from 30% to 70% and a 12-hr light/dark cycle. Animals were individually identified using picric acid marking along with cage and animal numbers. Standard rodent pellet feed and RO (Reverse Osmosis) water were provided ad libitum throughout the study period.

Preparation of Experimental animals

The mice were randomly assigned to five groups, each containing six animals, and were treated as given in Table 2.

Eddys Hot Plate Method

The hot plate test was used to measure the response latency time according to the 1953 methodology described by Eddy and Leimbach. Only mice that showed a nociceptive reaction within 15 sec were selected for the study. There was a 15-sec cut-off time

Table 1: Ingredients of *Ettikottai Mathirai*.

Sl. No.	Ingredients	Botanical name	Part used	Quantity
1	Milagu	*Piper nigrum*	Seed	1 Palam
2	Chukku	*Zingiber officinale*	Rhizome	1 Palam
3	Ettikottai	*Strychonos nux-vomica*	Seed	1 Palam
4	Lavangam	*Syzygium aromaticum*	Flower bud	1 Palam
5	Lemon juice	*Citrus lemon*	Fruit	1 Palam

for the hot plate latencies. The mice that had fasted overnight were given test medications orally through gastric gavage tubes that were suspended inside the vehicle. The normal drug (XX mg/kg) was administered intraperitoneally with an injection. The animals were set up on a 55°C heated metal plate that was enclosed by a Plexiglas cylinder with a diameter of 26 cm. Response latency is the amount of time, in seconds, that elapsed from the moment the animal was placed on the hot plate to the moment it started to shake, lick its back paws, or leap off the ground. The test's specificity and sensitivity were raised by measuring the reaction time of the first triggered behavior, regardless of whether it was paw licking or jumping. The reactions were measured at 0, 60, 90, and 120 min.[10]

"The percentage protection against thermal pain stimulus was calculated using the following formula:

% Protection=Test Mean-Control Mean/Test Mean×100"

RESULTS AND DISCUSSION

Analgesic activity

The results of analgesic activity using Eddy's hot plate method are presented in Table 3 and Figure 1.

The present study demonstrated that *Ettikottai Mathirai* (EM), a traditional Siddha polyherbal formulation, possesses significant central analgesic activity, as evidenced by the increased reaction times observed in Eddy's hot plate method. Both low (8.5 mg/kg) and high (17 mg/kg) doses of EM exhibited a dose-dependent increase in pain threshold when compared to the control group. Notably, the high dose of EM produced latency times comparable to that of the standard opioid analgesic pentazocine (5 mg/kg), suggesting a centrally mediated analgesic effect. The hot plate model primarily evaluates supraspinal responses, indicating that EM may act through central nervous system pathways. The analgesic effect of EM can be attributed to the synergistic actions of its herbal components, including *Piper nigrum, Zingiber officinale, Strychnos nux-vomica*, and *Syzygium aromaticum*, which are well-documented for their anti-inflammatory and analgesic properties. Traditional Siddha purification methods and the use of adjuvants such as water and buttermilk may enhance bioavailability and reduce potential toxicity, particularly of *Strychnos nux-vomica*.

Pain associated with inflammation involves a complex interplay of chemical mediators such as histamine, serotonin, bradykinin, prostaglandins, and leukotrienes. In the early phase of inflammation (0-4 hr), histamine and serotonin contribute to increased vascular permeability and nociceptor sensitization,

Table 2: Selection of Experimental Animals for analgesic activity of VRM in Swiss albino mice.

Sl. No.	Groups	Interventions	No. of animals
1.	Group-I (Vechile Control)	Control (Water) 2 mL/kg p.o	5 Male
2.	Group-II (Standard)	Pentazocine 5 mg/kg p.o	5 Male
3.	Group-III (Low dose)	EM 8.50 mg/kg p.o+water p.o	5 Male
4.	Group-IV (High dose)	EM 17 mg/kg p.o+Water p. o	5 Male
Total animals			20 Males

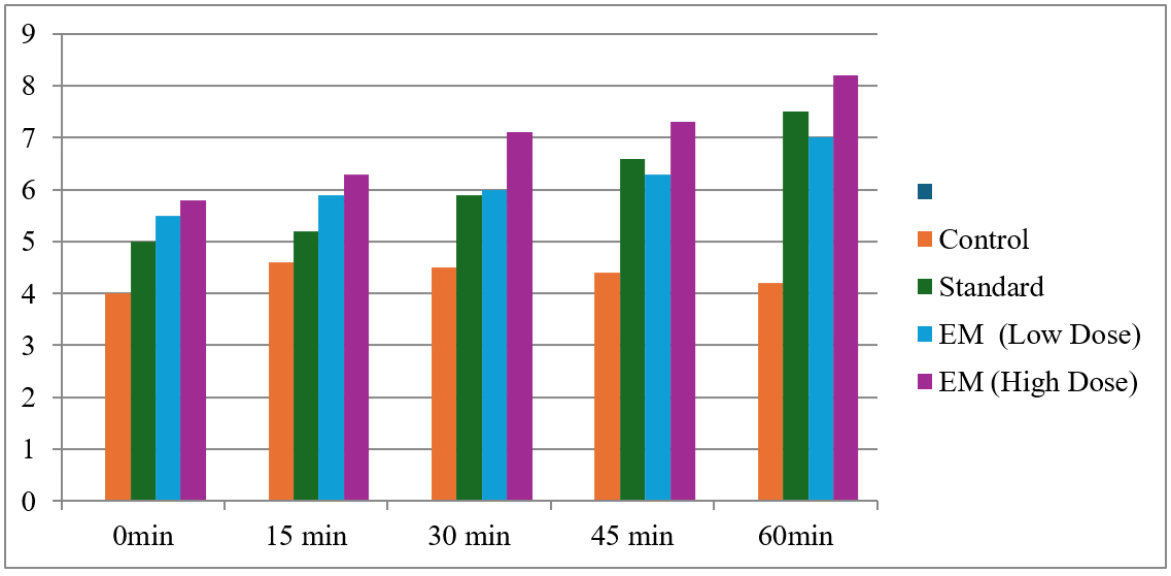

Figure 1: Results of Analgesic Activity in EM.

Table 3: Results of Analgesic Activity in EM.

Groups	0 min	15 min	30 min	45 min	60min
	Measurements are recorded in seconds				
Control	4.0	4.6	4.5	4.4	4.2
Standard	5.0	5.2	5.9	6.6	7.5
EM (Low Dose)	5.5	5.9	6.0	6.3	7.0
EM (High Dose)	5.8	6.3	7.1	7.3	8.2

promoting pain perception. Prostaglandins, particularly PGE2, play a central role in the sensitization of sensory neurons and are major targets of NSAIDs. In the later phase (3-5 hr), infiltration of polymorphonuclear leukocytes and the continued release of bradykinin and leukotrienes further perpetuate inflammation and pain.[11,12] Therefore, the observed analgesic effect of EM may be attributed not only to central nervous system modulation but also to potential inhibition of inflammatory mediators, highlighting its dual analgesic and anti-inflammatory properties. These findings provide scientific validation for the traditional use of EM in managing pain, especially in conditions classified under Vaatha diseases in Siddha medicine, and support its potential as an effective and safer alternative to conventional analgesic therapies.

CONCLUSION

The findings of this study scientifically support the traditional use of *Ettikottai Mathirai* as an effective analgesic agent in Siddha medicine. EM demonstrated a dose-dependent analgesic effect, particularly at higher doses, comparable to standard pharmaceutical agents. Its potential dual action-central analgesic and peripheral anti-inflammatory-positions it as a promising alternative for pain management. Further pharmacological investigations and clinical trials are needed to explore its mechanisms and establish its therapeutic safety and efficacy in humans.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ETHICAL APPROVAL

Before initiating the preclinical evaluation, the study procedure was granted ethical approval by the Institutional Animal Ethics Committee (IAEC) of the Centre for Laboratory Animal Technology and Research, Sathyabama Institute of Science and Technology, Sholinganallur, Chennai, Tamil Nadu-600119, India. All procedures adhered to the guidelines and ethical principles for animal experimentation under appropriate care and control. The IAEC approval number for this study is SU/CLATR/IAEC/XXII/17/2024 dated 02.03.2024.

ABBREVIATIONS

EM: *Ettikottai Mathirai*; **NSAIDs:** Non-Steroidal Anti-Inflammatory Drugs; **IAEC:** Institutional Animal Ethics Committee; **RO:** Reverse Osmosis; **p.o:** Per Oral.

AUTHOR CONTRIBUTION

Conceptualization: KS; Medicine Preparation: KS; Data collection and compilation: KS and SR; Manuscript Writing: KS and SR; Proofreading and editing: KS, SR, PS, CP and MA.

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