ANALGESIC EFFECT OF THE ETHANOLIC *STERCULIA GUTTATA* EXTRACT IN THERMAL AND CHEMICAL MODELS OF NOCICEPTION IN WISTAR RATS

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ABSTRACT

Context: A picture of the development of early sensory circuits in the growing dorsal horn of the spinal cord, and their capacity to receive nociceptive and non-nociceptive information, has been provided by peripheral and central nociceptive neurons route tracing electrophysiology**.** A group of specialised nociceptive afferents, which encode the severity of the experienced pain by their discharge strength, communicate acute mechanical, thermal, and chemically produced sensations in the skin. Recent research have discovered important molecular mechanisms for these processes. There hasn't been a successful therapeutic therapy for pain found in contemporary medicine as of yet. Many therapeutic plants remain unknown, and plant products are being examined to determine their ability to treat the impression of a painful or harmful stimuli.

Objective: In the current study, which is thought to be the first to use animal models, the analgesic impact of Sterculia guttata's ethanolic extract (ESG) is examined in thermal and chemical nociception models in Wistar rats.

Methods: Sterculia guttata bark was used to make the ethanolic extract (ESG), and its anti-inflammatory and anti-nociceptive properties were studied. Eddy's hot plate test and the tail immersion test were used to assess the anti-inflammatory activity, while acetic acid-induced writhing in Wistar rats was used to assess the analgesic effects

Results: The outcomes showed that Sterculia guttata bark ethanolic extract (ESG) has strong, dose-dependent anti-inflammatory and anti-nociceptive properties. Additionally, the extract decreased pain episodes and prevented acetic acid-induced discomfort in Wistar rats.**Conclusion:** From the study, it was observed that ethanolic extract of *Sterculia guttata* (ESG) in thermal and chemical models of nociception

Keywords: *Sterculia guttata* extracts, anti-nociceptive activity, anti-inflammatory activity thermal and chemical models.

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INTRODUCTION:

Afferents that specifically encode the intensity of the pain by the strength of their discharge are used to detect acute mechanical, thermal, and chemical sensations in the skin. Numerous changes in the primary afferent's characteristics take place concurrently with significant changes in the central nervous system after tissue inflammation or damage. (1) Alterations in the characteristics of primary nociceptive afferents can explain primary hyperalgesia, but functional changes in the central nervous system are absolutely necessary for secondary hyperalgesia. Numerous chemical mediators are produced by non-neuronal cells during inflammation and act on nociceptive neurones. In the end, the activity of membrane ion channels regulates the discharges from the neurones. The 5-hydroxytryptamine, ATP, and protons in the chemical mediator operate on receptors directly connected to ion channels. (2) Other mediators, like as bradykinin, work in an indirect manner by modulating the activity of ion channels and either activating neurons through receptors connected to second messenger systems. The several cell types that generate eicosanoids have crucial intra- and intercellular functions in nociception. Given that several non-neuronal cell types express receptors for sensory neuropeptides, interactions between neurones and non-neuronal cells are anticipated to be complicated (substance P). Additionally, recent research suggests that growth factors and cytokines may have long-term impacts on nociceptive neuron function. (3)

Herbal drug Profile:

Strerculia guttata Roxb:

Strerculia guttata Roxb common name bloody drop ordure tree, the synonym *Astrodendrum malabaricum* Dennst. *Clompanu malabarica* (Dennst.) Kuntze, *Sterculia alata* Wall. *Sterculia cuneata* Heyne, and it belongs to *Malvaceae juss* family. *Sterculia guttata* vernacular names are in Hindi- Hirik; Malayalam- Aanathondimaram; Tamil - Kavalam and in Kannada-Happu savage. The taxonomical classification of *Sterculia guttata* Roxb are Root- (Root); Kingdom - (Plantae); Phylum- (Tracheophyta); Class- (Equisetopsida C.Agardh); Order - (Malvaceae Juss); Family - (Malvaceae Juss); Genus-(Sterculia) and Species-*Sterculia guttata* Roxb. (4)

A crucial medicinal tree called Sterculia guttata Roxb. (Sterculiaceae) may be found in Assam, Maharashtra, and the Andaman and Nicobar Islands. It may grow to a height of 20 metres and is a deciduous tree. Habit are deciduous trees that may grow to a height of 20 metres; its bark is greyish-brown in colour and flaky when it is old. Young branchlets are stellate, terete, and tawny tomentose. The leaves are alternate, simple, and spirally clustered at the ends of the twigs. The stipules are enisform, caduceous, and leave scars. The petiole is 2 to 5 cm long, stellate, tawny tomentose, and swollen at both ends. The lamina is 8 to 24 cm long, 6.5 to 14 cm wide, and elliptic-ob Flowers are produced in densely stellate, terminal or axillary racemes; they are polygamous, white with pink spots, and have a 0.3 cm long pedicel. (5)

The fruit and seed follicles are composed of 1 to 5 woody, obovoid, 7.6 cm long, brilliant red or scarlet, and stellate villous that are pink or scarlet inside. The seeds are numerous, ovoid, and black. Streptococcus guttataThe proximate composition of the seed was examined for its nutritional relevance, and the results, expressed as a percentage of dry matter (DM), are: crude protein 21.40 ± 0.4, crude lipid 11.58± 0.2, crude fibre 7.73±0.5, carbohydrate 21.03±0.4, and moisture content 16.42±0.2, the mineral composition was as follows (mg/100gm of DM) Calcium 108.00±0.4, Potassium 105±0.5, Magnesium 59±0.2, Manganese (ppm) 19.66±0.5, Zinc (ppm) 18.74±0.3, Copper (ppm) 8.69±0.5, Iron (ppm) 27.12±0.4, Sodium 28.41±0.5.

The pharmaceutical importance for treating anxiety and sleep problems, as well as larvicidal action, filarial vector Culex quinquefasciatus and Aedes aegypti, the dengue disease vector. Previous studies have shown that Sterculia guttata seeds have CNS depressive, anti-epileptic, and mosquito larvacidal effects. (6) This work is thought to be the first to use animal models to investigate the analgesic efficacy of the ethanolic sterculia guttata extract in thermal and chemical models of nociception in wistar rats.

Animals

Adult Wistar rats of either sex (weighing between 150 and 200 g) were purchased from the University College of Veterinary and Animal Houses in Mannuthy, Kerala, and kept in the Central Animal House at the JKK Munirajah Medical Research Foundation Annai JKK Sampoorani Ammal College of Pharmacy (approved number: 1158/CPCSEA) with 12-hour cycles of light and darkness. The trial's normal meal consisted of pellets from Sri Venkateshwara Enterprises in Subramanya Nagar, Bangalore, India. Both the control and experimental animals received access to food and water at any time. All animal tests were conducted in conformity with the CPCSEA's ethical guidelines (Ethical Committee IAEC reg no. JKKMMRFCP/IAEC/2021/019).

Values are expressed as the mean ± SEM from 6 animals in each group; differences in means were estimated by using one-way ANOVA followed by Dunnet's post hoc test. The values of Group II, III, IV and V were compared with Group I. *P<0.05 = significant, **P<0.01 = moderately significant, ***P<0.001= highly significant, ns = non significant.

Experimental group

Ethanolic *Sterculia guttata* (ESG) bark extracts were prepared extract was tested the screening of analgesic activity of ESG (200 & 400 mg/kg, p.o.) were done in 4 different groups (n=6/group) of rats. The following Table No: 1 shows the grouping pattern of rats and drug treatment used for the evaluating analgesic activity by Eddy's hot plate, tail immersion and acetic acid-induced writhing tests respectively.

Table No: 1 Grouping of animals for analgesic activity of ESG in Eddy's hot plate and tail immersion tests

S. No.	Treatment groups	Rats treated with
1	Group I (Control)	CMC 0.5 % suspension (1 ml/kg, p.o.)
2	Group II (Standard)	Pentazocine (10 mg/kg, i.p.)
3	Group III	ESG (200 mg/kg, p.o.)
4	Group IV	ESG (400 mg/kg, p.o.)

Procedure:

1. Study of analgesic activity of ESG in rats by Eddy's hot plate test

The test scrutinize the analgesic effect of test compounds or agents that acts centrally to acute thermal stimulus. Eddy's hot plate is made up of an electrically heated surface of copper, conserved at a temperature of about 55 ± 5^0 C inside a restraining cylinder. The paws of rats are usually highly reactive to heat at temperatures which are not hurtful to their skin. The responses like jumping and paw withdrawal or paw licking was considered as nociception indicators. The time elapse for these responses was prolonged by centrally acting analgesics, whereas peripheral analgesics do not afflicted these responses. Group I rats served as control treated with CMC 0.5 % suspension, 1 ml/kg/p.o. Group II served as standard received Pentazocine (10 mg/kg, i.p.), group III received ESG (200 mg/kg, p.o.), and group IV received ESG (400 mg/kg, p.o.) respectively.

Rats from respective groups were placed individually on the hot plate. The time interspaces between placing the rat on the hotplate and either paw response (paw licking) and or jumping response from the hot surface (indication of pain) were recorded as reaction time manually using a stopwatch. A cut off time of 15 sec was pursued to avoid thermal injury to rat paws. The reaction time was calculated at 0 min, 30 min, 60 min and 90 min following the administration of CMC suspension, pentazocine, ESG respectively, and the results were done statistically (**7**). The results are given in Table No: 3 and in the FIG: 1.

2. Study of analgesic activity of ESG in rats by tail immersion test

Tail immersion test is gleaned from the fact that morphine-like centrally acting drugs are particularly capable of protracting the reaction time of classic tail-withdrawal reflex in rats. **ESG** was screened for their analgesic effect actuated by sinking tail of rats (lower 5cm), gently in heated water controlled at 55 ± 5^0 C, after marking. Within a few Sec, rat reacted by withdrawing its tail. The rats that raised their tail from heated water within 5 sec time limit were selected for the study. Group I rats served as control treated with CMC 0.5 % suspension, 1 ml/kg/p.o. Group II served as standard received pentazocine (10 mg/kg, i.p.), group III received ESG (200 mg/kg, p.o.), and group IV received ESG (400 mg/kg, p.o.) respectively. Rats from different groups received CMC suspension (0.5 % w/v), Pentazocine, ESG, respectively, just before the study and the reaction time (time taken for a rat to lift the tail from hot water) was noted at 0 min, 30 min, 60 min and 90 min, manually using a stopwatch.

A cut off time of 15 sec was maintained thought out the study to escape rat from tail injury and the tail of the rat was dried after each determination. A withdrawal time that exceeding 6 sec was witnessed as a positive response (8, 9). The results are given in Table No: 4 and in the FIG: 2.

3. Study of analgesic activity of ESG in rats by acetic acid-induced writhing test

Acetic acid induced writhing test is broadly used as a simple screening method to assess the analgesic substances those attain effects, peripherally. Rats react with a unique behavioral stretch, extension of hind limbs, and constriction of abdomen where the abdomen touches the floor and turning of trunk (twist), called as writhes. Group I rats served as control treated with CMC 0.5 % suspension, 1 ml/kg/p.o. Group II served as standard received indomethacin (10 mg/kg, p.o.), group III received ESG (200 mg/kg, p.o.), and group IV received ESG (400 mg/kg, p.o.) respectively. Rats from different groups were pretreated with CMC suspension, ESG and indomethacin, 30 min before the i.p injection of 0.7% acetic acid solution (10 ml/kg), respectively.

The rats were then retained in separate transparent boxes, individually and observed for number of writhes (abdominal constrictions) that exist for next 20 min time period. Significant reduction in number of writhes in tested animals as compared to the control animals was recorded as confirmation for the presence of analgesia **(10).**

The Percentage inhibition was computed using the formula:

$$\% \text{ Inhibition } = \frac{Mc - Mt}{Mc} \text{ X } 100$$

Where, Mc = Mean number of writhes in the control group, Mt = Mean number of writhes in test group. The results are given in **Table No: 2** and in the **FIG: -3**

Table No: 2 Grouping of animals for analgesic activity of ESG in acetic acid-induced writhing test

S. No.	Treatment groups	Rats treated with
1	Group I (Control)	CMC 0.5 % suspension (1 ml/kg, p.o.)
2	Group II (Standard)	Indomethacin (10 mg/kg, p.o.)
3	Group III	ESG (200 mg/kg, p.o.)
4	Group IV	ESG (400 mg/kg, p.o.)

RESULTS OF ANALGESIC ACTIVITY

Results of analgesic activity of ESG **in rats by Eddy's hot plate test**

Table No: 3 Results of analgesic activity of ESG **in rats by Eddy's hot plate test**

Group/Treatment	Reaction Time (Sec)			
	0 min	30 min	60 min	90 min
Group – I (Control - CMC 0.5 % suspension - 1 ml/kg, p.o.)	4.224±0.243	4.124±0.6237	4.215±0.4153	4.314±0.4269
Group – II (Pentazocine - 10 mg/kg, i.p.)	4.233±0.7032^{ns}	9.783±0.912***	10.943±1.065***	11.624±0.246***
Group – III (ESG 200 mg/kg, p.o.)	4.025±0.4126^{ns}	6.237±0.8224 ^{ns}	6.243±0.5438 ^{ns}	8.612±0.6356*
Group – IV (ESG 400 mg/kg, p.o.)	4.367±0.4382^{ns}	7.654±0.5486*	8.489±0.5427*	9.3547±0.3409**

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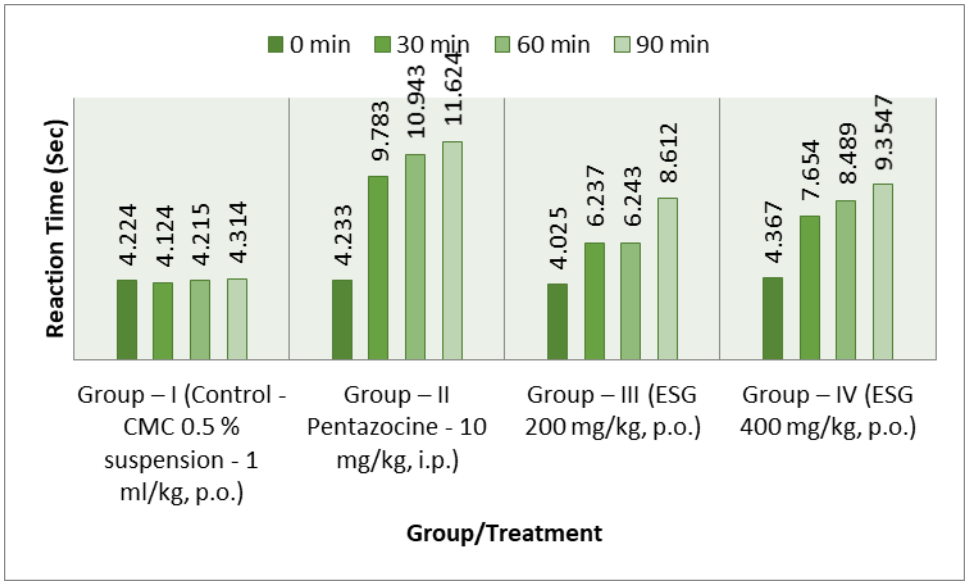

FIG: 1 Diagrammatic representation of analgesic activity of ESG in rats by Eddy's hot plate test

Table No:1 and **FIG:1** represented the results of analgesic activity for ESG in rats by Eddy's hot plate test, the mean reaction time of each group of rats at the time intervals 0, 30, 60, and 90 min, respectively. Group II rats treated with the standard drug, pentazocine (10 mg/kg, i.p.) showed high significant (P<0.001) increased in reaction time at 30, 60 and 90 min of 9.783±0.912 Sec, 10.943±1.065 Sec and 10.943±1.065 Sec, except 0 min of 4.233±0.7032 Sec, with non-significant effect compared to group I control rats treated with CMC 0.5 % suspension (1 ml/kg, p.o.).

The reaction time of group I rats at 0, 30, 60, and 90 min was found as 4.224±0.243 Sec, 4.224±0.243 Sec, 4.215±0.4153 Sec and 4.314±0.4269 Sec, respectively. Group III rats treated with ESG (200 mg/kg, p.o.) showed less significant (P<0.05) increased in reaction time of 8.612±0.6356 Sec only at 90 min despite of non-significant increase in 0, 30 & 60 min of reaction time of 4.025±0.4126

Sec, 6.237±0.8224 Sec and 6.243±0.5438 Sec with respect to control group of rats.

Contemporarily, group IV rats treated with ESG, (400 mg/kg, p.o.), showed less and moderate significant (P<0.05 and <0.01) increase in mean reaction time of 7.654±0.5486 Sec, 8.489±0.5427 Sec and 9.3547±0.3409 Sec at all-time intervals of 30, 60 and 90 min except 0 min of 4.367±0.4382 with non-significant effect.

Results of analgesic activity of ESG **in rats by tail Immersion test**

Table No: 4 Results of analgesic activity of ESG **in rats by tail immersion test**

Group/Treatment	Reaction Time (Sec)			
	0 min	**30 min**	**60 min**	**90 min**
Group – I (Control - 0.5 % CMC - 1 ml/kg, p.o.)	3.012±0.423	3.532± 0.235	3.811± 0.438	4.091± 0.756

Group – II (Pentazocine - 10 mg/kg, i.p.)	3.812±0.423^{ns}	7.133± 0.854**	9.045±0.734***	10.552±0.623***
Group – III (ESG - 200 mg/Kg, p.o.)	3.515±0.435^{ns}	5.958± 0.612^{ns}	6.523± 0.745^{ns}	8.135± 0.822**
Group – IV (ESG - 400 mg/Kg, p.o.)	3.633±0.423^{ns}	6.325± 0.775*	8.167±0.123**	9.345±0.868**

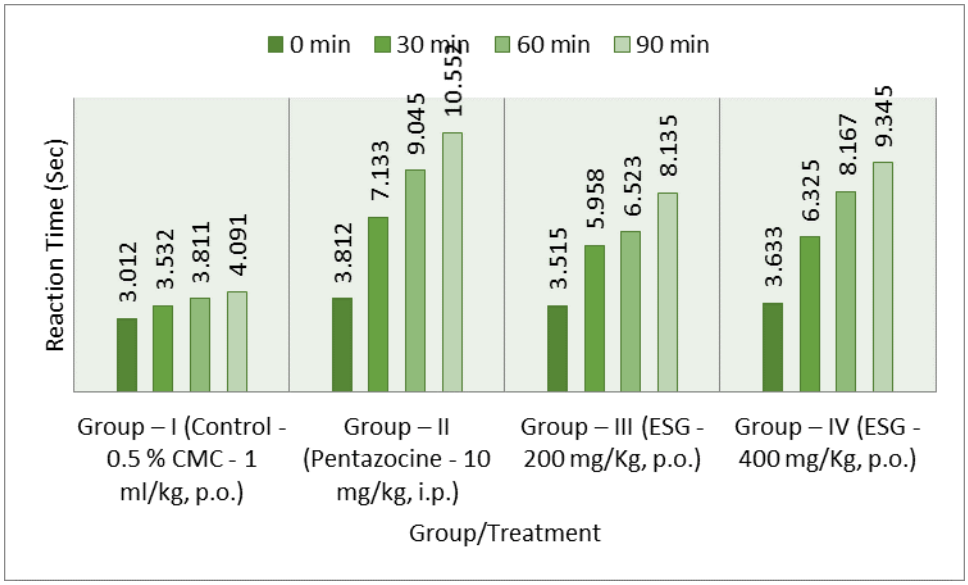

FIG: 2 Diagrammatic representation of analgesic activity of ESG in rats by tail immersion test

In tail immersion test (Table No: 1 and FIG: 1), group II rats treated with the standard drug, pentazocine (10 mg/kg, i.p.) showed moderate and highly significant (P<0.01 and P<0.001) increased in reaction time at 30, 60 and 90 min of 7.133± 0.854 Sec, 9.045±0.734 Sec and 10.552±0.623 Sec, except 0 min of 3.812±0.423 Sec with non significant effect compared to group I control rats treated with 0.5 % w/v CMC suspension (1 ml/kg, p.o.). The reaction time of group I rats at 0, 30, 60, and 90 min were found to be 3.012±0.423 Sec, 3.532± 0.235 Sec, 3.811± 0.438 Sec and 4.091± 0.756 Sec, respectively.

Group III rats treated with ESG (200 mg/kg, p.o.) showed less significant (P<0.05) increased in reaction time of 8.135± 0.822 Sec only at 90 min despite of non significant increased in 0, 30 & 60 min of reaction time of 3.515±0.435 Sec, 5.958± 0.612 Sec and 5.958± 0.612 Sec with respect to control group of rats.

The group IV rats treated with ESG (400 mg/kg, p.o.), showed less and moderate significant (P<0.05 and <0.01) increased in mean reaction time of 6.325± 0.775 Sec, 8.167±0.123 Sec and 8.167±0.123Sec at all time intervals of 30, 60 and 90 min except in the 0 min was 3.633±0.423 Sec with non significant effect.

Results of analgesic activity of ESG **in rats by acetic acid-induced writhing test**

Table No: 5 Results of analgesic activity of ESG in rats by acetic acid-induced writhing test

Group/Treatment	**Number of Writhes**	**% Inhibition**
Group – I (Control - 0.5 % CMC - 1 ml/kg, p.o.)	35.50± 3.481	00
Group – II (Indomethacin - 10 mg/kg, p.o.)	10.33± 1.764***	70.901
Group – III (ESG - 200 mg/Kg, p.o.)	21.67± 2.603**	38.957
Group – IV (ESG - 400 mg/Kg, p.o.)	13.17± 2.136**	62.901

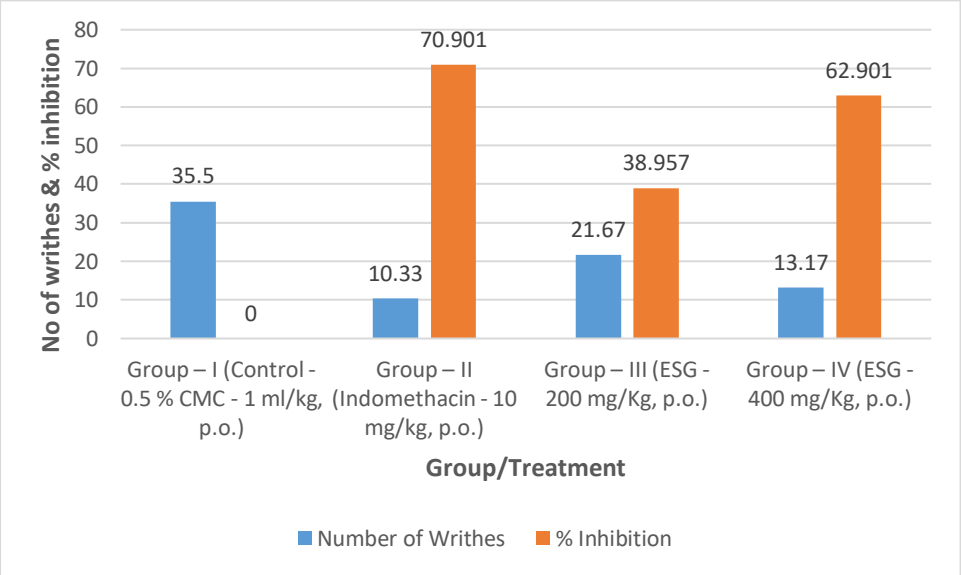

FIG: 3 Diagrammatic representation of analgesic activity for the ESG in rats by acetic acid-induced writhing test

In this screening of analgesic activity for the ESG in rats by acetic acid-induced writhing test (Table No:5), group II rats treated with standard drug, indomethacin (10 mg/kg, p.o.) shown highly significant (P<0.001) decreased in number of writhes (10.33± 1.764) compared to group I control rats of 35.50± 3.481 treated with 0.5 % w/v CMC (1 ml/kg, p.o.), respectively. Group III and group IV rats treated with DI (100 mg/kg, p.o.) and ESG (400 mg/kg, p.o.), individually, showed moderately significant (P<0.01) decreased in mean number of writhes as 21.67± 2.603 and 13.17± 2.136 respectively.

In current study, both central and peripheral analgesic effect of ESG was detected by Hot plate test, tail immersion test and acetic acid-induced writhing test on Wistar rats. Pain arises as a natural manifestation with a typical perception involving central and peripheral mechanisms and is normally a distasteful effect, produced due to an influx of nerve impulses that are engendered by noxious stimuli. (**11**).

Drugs used in controlling or removing pain, are called analgesics, they can relieve or reduce pain by acting on nociceptors present in either central nervous system (CNS) or in periphery without much influence on other perceptions. Nociceptors are functional nerve endings that respond directly

to noxious stimuli and indirectly to chemicals including histamine, bradykinin, serotonin, acetylcholine, substance P and few peptides which are liberated from injured tissues, devoting to neurogenic pain. The periodically accepted animal models to learn analgesics includes pain-state models that uses thermal, chemical, mechanical and electric stimuli as their basis (**12**).

Hot plate test and tail immersion test are the popular tests of nociception banking on evocation of pain by high intensity of thermal stimulus. These are the extensively used models to evaluate central analgesic activity of therapeutic compounds deputing on descending inhibitory pathway at spinal and supraspinal levels. These tests are useful to discriminate central opioid-like analgesics from peripheral analgesics. The jumping or paw-licking response which is rated in hot plate test is highly complexes, and mediated as supraspinal reflex, while the tail-withdrawal response in tail immersion test is mediated spinally.

The pain produced by thermal stimulus in both tests is restricted to centrally mediated nociception through opioid receptors, and are highly potent in synchronizing thermal pain. Stimulation of these receptors is connected to pain relief, producing spinal or supraspinal analgesia. The two enkephalins, namely met- and leu-enkephalins are the cardinal endogenous opioids found in spinal cord and brain stem, which are involved in analgesia **(13).**

The results of this study disclosed that ESG as well as Pentazocine showed remarkable analgesic effect against thermally instigated pain through the hot plate and tail immersion. The significant increase in pain threshold effected by ESG, individually at a dose of 200 mg/kg, orally counseled their implication among pain pathways mediated centrally through opioid receptors in spinal and supraspinal regions of nervous system. However, ESG administered individually at a dose of 200 mg/kg, p.o. have showed significances in analgesic effect only at 90 min.

An irritant like acetic acid can induce pain impulses peripherally upon their injection on rats. Acetic acid-induced writhing test is a chemically induced nociceptive model in which the abdominal constriction called writhes is generated by i.p injection of acetic acid and is one among the repeated models for classify in

agents of peripheral active analgesics (**14**). Acetic acid when delivered directly into peritoneal cavity of rat liberates several endogenous mediators of pain such as serotonin, histamine, prostaglandins (PGE2 and PGF2α), bradykinins and substance P. These endogenous mediators after release, in peritoneum, interact with local pain receptors cause excitation of nerve endings which are responsible for pain and results in abdominal constriction (writhing response). Induction or stimulation of this peripheral nociceptive mechanism (signal transduction) possibly been impaired and weakened by analgesics thereby decreasing the number of writhes (**15**).

The percentage inhibition of number of writhes registered from this study revealed that ESG exhibited a more prominent peripherally-mediated analgesic activity, which may be due to the inhibition of synthesis and action of prostaglandins, substance P and other endogenous substances which are key players in pain production.

A distinct network for nociceptive modulation has just recently been identified, despite the fact that efferent regulation of sensory transmission is a well-established notion. Midbrain, medullary, and spinal level components of this network are interrelated. Electrical stimulation of the periaqueductal grey (p.a.g.) reduces nociceptor-induced reflexes and escape behaviour in a number of species at the midbrain level by inhibiting spinal neurons that react to noxious stimuli. (16) In individuals with

clinically substantial pain, midbrain stimulation also results in analgesia. Similar behavioural and physiological effects are produced by the rostral ventral medulla (r.v.m.), which also mediates midbrain antinociceptive activities at the spinal cord level. At every level of this nociceptive regulating network, endorphins are present. Opiate microinjections at the p.a.g., r.v.m., or spinal levels result in analgesia, likely through imitating endorphin activities. Whether activated by opiates or electrical stimulation, the nociceptive modulatory system is diffusely structured, highly linked, and seems to function as a single entity. (17) Pentazocine, however, stimulate the off-cell and block the firing of the on-cell when administered systemically or through the p.a.g. The r.v.m. output cell, which blocks nociceptive transmission at the spinal cord level, is most likely the off-cell. Uncertainty surrounds the on-purpose. cell's Numerous stressful environmental circumstances, which are frequently but not always unpleasant, can cause the nociceptive modulator system to become active. (18)

CONCLUSION

In conclusion, ESG showed significant analgesic effect in all the three established experimental models of pain in thermal and chemical models of nociception in Wistar rats. Their action was likely to be mediated both centrally through stimulation of opioid receptors and peripherally against endogenous pain inducers.

REFERENCES

1. Koltzenburg M. Neural mechanisms of cutaneous nociceptive pain. The Clinical journal of pain. 2000 Sep 1;16(3 Suppl):S131-8.
2. Rang HP, Bevan S, Dray A. Chemical activation of nociceptive peripheral neurones. British Medical Bulletin. 1991 Jul 1;47(3):534-48.
3. Levi-Montalcini R, Skaper SD, Dal Toso R, Petrelli L, Leon A. Nerve growth factor: from neurotrophin to neurokine. Trends in neurosciences. 1996 Nov 1;19(11):514-20.
4. El-Sherei MM, Ragheb AY, Kassem ME, Marzouk MM, Mosharrafa SA, Saleh NA. Phytochemistry, biological activities and economical uses of the genus Sterculia and the related genera: A reveiw. Asian Pacific journal of tropical disease. 2016 Jun 1;6(6):492-501.
5. Ramachandran VS. Wild edible plants of the Anamalais, Coimbatore district, western Ghats, Tamil Nadu.
6. Badami RC, Patil KB, Subbarao YV, Sastri GS, Vishvanathrao GK. Cyclopropenoid fatty acids of sterculia oils by gas liquid chromatography. Fette, Seifen, Anstrichmittel. 1980;82(8):317-8.
7. Patel PK, Sahu J, Chandel SS. A detailed review on nociceptive models for the screening of analgesic activity in experimental animals. Int J Neurol Phys Ther. 2016;2(6):44.
8. Bhattacharya A, Agrawal D, Sahu PK, Kumar S, Mishra SS, Patnaik S. Analgesic effect of ethanolic leaf extract of Moringa oleifera on albino mice. Indian Journal of Pain. 2014 May 1;28(2):89.
9. Sasikala V, Saravanan S, Parimelazhagan T. Analgesic and anti–inflammatory activities of Passiflora foetida L. Asian Pacific journal of tropical medicine. 2011 Aug 1;4(8):600-3.
10. Gawade S. Acetic acid induced painful endogenous infliction in writhing test on mice. Journal of Pharmacology and Pharmacotherapeutics. 2012 Oct 1;3(4):348.
11. Blakely WR, Page GG. Pathophysiology of Pain in Critically III Patients. Critical care nursing clinics of North America. 2001 Jun 1;13(2):167-79.
12. McKune CM, Murrell JC, Nolan AM, White KL, Wright BD. 29 Nociception and Pain. Veterinary anesthesia and analgesia. 2015 Mar 30:584.
13. Chapman CR, Vierck CJ. The transition of acute postoperative pain to chronic pain: an integrative overview of research on mechanisms. The Journal of pain. 2017 Apr 1;18(4):359-e1.
14. Abbah J, Amos S, Chindo B, Ngazal I, Vongtau HO, Adzu B, Farida T, Odutola AA, Wambebe C, Gamaniel KS. Pharmacological evidence favouring the use of Nauclea latifolia in malaria

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ethnopharmacy: effects against nociception, inflammation, and pyrexia in rats and mice. Journal of Ethnopharmacology. 2010 Jan 8;127(1):85-90.

15. Chen L, Yang G, Grosser T. Prostanoids and inflammatory pain. Prostaglandins & other lipid mediators. 2013 Jul 1;104:58-66.
16. Fields HL, Heinricher MM. Anatomy and physiology of a nociceptive modulatory system. Philosophical Transactions of the Royal Society of London. B, Biological Sciences. 1985 Feb 19;308(1136):361-74.
17. Haghparast A, Gheitasi IP, Lashgari R. Involvement of glutamatergic receptors in the nucleus cuneiformis in modulating morphine-induced antinociception in rats. European journal of pain. 2007 Nov 1;11(8):855-62.
18. McGrath PA. Psychological aspects of pain perception. Archives of oral biology. 1994 Jan 1;39:S55-62

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