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Original Research Article

Pharmacological investigation of *Thespesea populnea* bark extract for analgesic activity

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ABSTRACT

Background: Pain is an unpleasant and distressing common problem with profound impact on individuals and society. Existing treatment modalities used for pain management are either less effective or exhibits several side effects. The aim of current study is to investigate the analgesic activity of stem bark extract of *Thespesea populnea* for pain management.
Methods: Thirty Swiss albino were divided into five groups including control, standard and three tests groups (different doses of *Thespesea populnea* bark extract). Groups were investigated for analgesic activity using hot plate induced paw withdrawal, acetic acid induced writhing and formalin induced paw licking models.
Results: Findings of hot plate model revealed that, percent increase in reflex latency of paw licking response in mice for test drug (10 mg/kg), attained peak effect of 136% at 180 minutes, whereas for standard pentazocine peak effect of 125% was attained at 180 minutes. In acetic acid model, the maximum percent inhibition in number of writhings for the test drug (30 mg/kg) was 68% and for standard diclofenac, it was 80%. In formalin model, percent inhibition in licking response in early and late phases for test drug (30 mg/kg) were 81% and 91% and for standard diclofenac it was 56% and 94% respectively. It was thus depicted that analgesic activity of test drug was significantly more than the standard in early phase and equivalent to standard in late phase.
Conclusions: It was concluded that *Thespesea populnea* bark extract at a dose of 10 mg/kg showed potential peripheral and central analgesic activity.

Keywords: Pain, Analgesic, Thespesea populnea, bark extract

INTRODUCTION

International association for the study of pain defines pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage".[1] Pain is a very common localized or generalized unpleasant bodily sensation associated with actual or potential tissue damage; pain is induced by a noxious stimulus and received by naked nerve endings.[2] Pain causes mild to severe physical discomfort such as pricking, throbbing and typically leads to evasive action and emotional distress. Perception of pain is transmitted to multiple cortical areas of the brain primarily by nociceptors.[3] The pain receptors are usually free nerve endings that are widespread in the superficial layers of the skin as well as in certain internal tissues such as periosteim, arterial walls, joint surfaces and cranial vault.[3,4] Activation of nociceptor nerves ocuurs due to thermal/mechanical/chemical stimulus, direct trauma or through release of mediators like bradykinins, prostaglandins, histamine, serotonin arachidonic acid, etc. from damaged tissues, initiates pain sensation.[5] Amount of mediators released, number of pain receptors stimulated and duration of stimulus defines the severity of pain. Myelinated A-delta type of nociceptor nerves are

responsible or rapid transmission of pain signal and are responsible for sharp pain sensation later changing to burning sensation or soreness.[6] Unmyelinated C type of nociceptor nerves transmits pain sensation slowly and is associated with deep aching or throbbing types of pain that follows the initial sharp pain.[5,6] Pain can be broadly classified as acute or chronic, or based on the origin of the injury or pain fibers as somatic or visceral nociceptive pain and neuropathic or sympathetic non nociceptive pain.[7] Somatic pain involves nociceptors originating in the peripheral tissues such as skin and muscles, while visceral pain originates in internal organs.[7] Visceral pain area is not well localized and frequently the pain sensation is referred to another area of the body.[7,8] Neuropathic pain occurs due to damage of peripheral nerve anywhere in the central nervous system, persistent or paroxysmal sharp pain is sensed along the distribution of that nerve even in the absence of a painful stimulus.[9]

A wide range of treatment modalities are used for pain management like opoids (e.g. fentanyl, oxycodone, morphine), non-steroidal anti-inflammatory drugs (e.g. acetaminophen, ibuprofen), analgesics (e.g. paracetamol, aspirin, capsaicin cream), topical and local anesthetics (e.g. lignocaine) and non-pharmacological treatments (e.g. psychotherapy or counseling), but multimodal treatment is considered as most beneficial in pain relief due to additive or synergistic effect of different modalities and the potential to reduce side effects of an individual treatment strategy.[10-12] Majority of existing treatment modalities for pain management exhibits several side effects like nausea, vomiting, skin rashes, liver damage, heart burn, upset stomach, dizziness, ringing in ears, heart/kidney failure, drowsiness, confusion, constipation etc., when taken in high or frequent dosing.[13-15] So current investigation was aimed towards finding a natural origin based novel treatment modality for pain management.

Thespesia populnea a genus of malvaceae, commonly known as papal/pipalo in local Indian languages is a large tree found in tropical and coastal forests of India (Figure 1).[17] Milo, *Hibiscus populnea*, Pacific rosewood, bebaru/baru baru are other synonyms used for *Thespesia populnea*, it is a common plant of coastal strands across world tropics. *Thespesia populnea* is a mangrove associate and plants provide shelter and food to many creatures of the mangroves.[18] *Thespesia populnea* is an evergreen tree which is bushy when young but thins out upon aging; it grows rapidly under favorable conditions up to a height of 13 m (40 ft) or more with a spread of 3-6 m (10-20 ft).[17-19] Bark of *Thespesia populnea* is brown, corrugated and have scaly twigs, leaves are shiny green and heart-shaped, usually ranging in size from 10 to 20 cm long and 6-13 cm broad. Cup-shaped hibiscus like pale yellow flowers (4 to 7 cm) with a dark blotch at the base of the petals that last for one to two days are seen on *Thespesia* populnea.[18] The flowers open close on same day, and the yellow flower turn dark red/purple as the day progresses. Fruits and seeds of *Thespesia populnea* includes a flattened indehiscent leathery sphere like capsules with disc like sepals that are green at first but turn brown and then black upon ripening and drying. The capsule usually has 8-15 grayish brown to black seeds that are 0.7 to 1.2 cm long.[17-19] Phytochemical investigations indicated that the ethanolic extract of *Thespesia populnea* bark contains alkaloids, carbohydrates, protein, tannins, phenols, flavonoids, gums and mucilage, saponins and terpenes. Gossypol was found to be the major component of *Thespesia populnea*; four naturally occurring quinines viz. thespone, mansonone-d, mansonone-H, thespone and thespesone have also been found in the extracts of heartwood of Thespesia populnea.[17-19]

Thespesia populnea has a wide range of uses ranging from medicinal uses to food plant to timber for crafts like utensils, containers and other carved objects. The plant is used as a shade tree and windbreak and also for producing ropes and dye.[17,18] Medicinally *Thespesia populnea* is reported to have anti-bacterial and anti-fungal properties and is useful in treating cutaneous infections, such as scabies, psoriasis, eczema, ringworm and guinea worm. Decoction of *Thespesia populnea* bark is commonly used for the treatment of skin and liver diseases and oil of bark mixed with vegetable oil is useful in treatment of urethritis and gonorrhea. The astringent activity found in bark, roots and fruits is used in dysentery, cholera, hemorrhoids and to heal wounds. The leaves of *Thespesia populnea* are reported to be anti-inflammatory, antinociceptive and are used in treating swollen joints. In addition published literature reports several other pharmacological activities like anti-oxidant, anti-fertility, anti-implantation, antisteroidogenic, anti-hyperglycemic and anti-diarrhoeal activities of extracts from different plant parts of *Thespesia populnea*.[20-27]

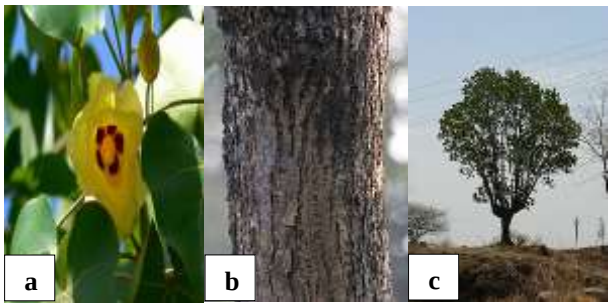


Figure 1: *Thespesia populnea* tree (a) aerial part, (b) whole tree and (c) bark.

Aim and objectives

Majority of existing treatment modalities for pain management exhibits several side effects, thus the aim of the present study was to determine the analgesic activity of stem bark extract of *Thespesea populnea* for pain management. The specific objectives of current study were to assess analgesic activity of the bark extract of *Thespesea populnea* using hot plate induced paw withdrawal reaction in mice, acetic acid induced writhing in mice and formalin induced paw licking in mice.

METHODS

Current investigation was conducted at department of pharmacology, PES institute of medical sciences and research, Kuppam.

Inclusion and exclusion criteria

Animals of either sex, weighing between 20-25 grams and animals exhibiting basal reaction time less than 10 seconds were included in the study. Animals weighing less than 20 grams or more than 30 grams and showing basal reaction time more than 10 seconds were excluded from the study.

Procedure

In current study Swiss albino mice of either sex weighing 20-25 g were selected and maintained for 7 days in the animal house under standard conditions of temperature (24±1°C), relative humidity (45-55%) and 12:12 light: dark cycle. The animals were fed with standard rat pellets and water ad libitum and were allowed to acclimatize to laboratory conditions 48 hours prior to commencing the experiment. Animals were subjected to model experiments like hot plate induced paw withdrawal test, acetic acid induced writhing test and formalin induced paw licking test to determine the analgesic activity of the bark extract of *Thespesea populnea*. For each test thirty mice weighing between 20-25 g were randomly divided into 5 groups; each group consisting of 6 animals, control group in all the tests were orally given 2% gum acacia, standard group in hot plate induced paw withdrawal test received pentazocine, intraperitoneally (25 mg/kg), for acetic acid induced writhing test and formalin induced paw licking test, the standard groups were orally given diclofenac sodium (10 mg/kg).

In all the experiments, test groups 1, 2 and 3 were orally given 3 mg/kg, 10 mg/kg and 30 mg/kg of bark extract *Thespesea populnea* respectively after suspending the extract in 2% gum acacia solution.

Hot plate induced paw withdrawal test

Eddy's hot plate was maintained at temperature of 55±1°C and the paw of mice was placed on the preheated hot plate, since the paw of mouse is very sensitive to heat at temperatures which are not skin damaging, latency time for responses like jumping, withdrawal of the paw from the hot plate or licking of the paw at the above mentioned temperature were recorded with the aid of a stop watch.

Time for the responses was expected to prolong after administration of centrally acting analgesics, whereas peripheral analgesics do not generally affect these responses. Observations were made at the time intervals of 60, 120 and 180 minutes following administration of the standard and the test compound with the cut off time of 15 seconds.

Acetic acid induced writhing test

Acetic acid induce pain when given through injection into the peritoneal cavity of mice and the animals start reacting with a characteristic stretching behavior called as writhing. After one hour of drug administration all the animals including the test and standard groups were intraperitoneally injected with acetic acid (0.1 ml/10g). Five minutes after the injection response of the animals in form of number of writhes was counted in individual mice for a period of 20 minutes. Numbers of writhes were expected to be reduced in groups administered with analgesics incomparision to control group. Percent protection against acetic acid induced writhing was calculated using the formula;

$$standard - control/control \times 100$$

Formalin induced paw licking test

In current study, formalin test has been proposed as a chronic pain model which is sensitive to both peripherally and centrally active analgesics. Pain responses in this model were indicated by elevation or favouring of the paw or excessive licking and biting of the paw. One hour post drug administration in standard and test groups, each mouse was subcutaneously given 0.1 ml of 1% formalin under the dorsal surface of the hind paw and was observed for licking response after 0-10 minutes and 20-30 minutes. Analgesics were expected to be effective if both paws of mice rested on the floor with no obvious favouring of the injected paw. Percent protection against formalin induced paw licking in mice was calculated using the formula;

$$standard - control/control \times 100$$

Statistical analysis

All the collected and observed data were statistically analyzed using ANOVA test followed by Dunnett's test.

RESULTS

Hot plate induced paw withdrawal test

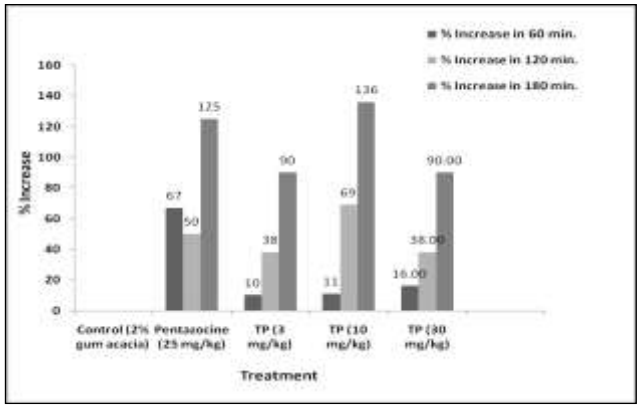
Pre-clinical observations made at time intervals of 60, 120 and 180 minutes post administration of the standard and test analgesic compounds in terms of licking of paw by mice in hot plate model are revealed in (Table 1). Latency time for licking response post 60 minutes in control and standard groups were observed to be 7.4±0.89 seconds and 12.33±0.71 seconds respectively. Paw licking latency time in the test group orally treated with 3 mg/kg, 10 mg/kg and 30mg/kg of bark extract *Thespesea populnea* were observed to be 7.00±0.5 seconds, 8.2±0.93 seconds and 8.6±1.70 seconds respectively post 60 minutes of extract administration. The overall all percent increase in paw licking latency time in standard and test groups when compared to control group are shown in (Figure 1). Similarly, latency time and percent increase in latency time

for paw licking response in mice post 120 and 180 minutes, in control, standard and test groups are depicted in (Table 1 and Figure 2). It was observed from the results of the investigations that the test extract of *Thespesea populnea* at 10 mg/kg concentration attained peak effect at 180 minutes and the effect declined at 60 minutes, whereas pentazocine treated group attained peak effect at 180 minutes.

Table 1: Latency time for paw licking response in mice observed in hot plate method.

Treatment groups	Latency time (seconds) of paw licking response observed at post treatment time intervals		
	60 minutes	120 minutes	180 minutes
Control	7.4± 0.89	7.8± 0.67	6.00±0.5
Standard (Pentazocine; 25mg/kg)	12.33±0.71	11.67±1.31	13.5±0.56**
Test group 1 (TP bark extract, 3 mg/kg)	7.00±0.5	10.2±0.73	11.4±0.98**
Test group 2 (TP bark extract, 10 mg/kg)	8.2±0.93	13.2±0.67**	14.2±0.53**
Test group 3 (TP bark extract, 30 mg/kg)	8.6±1.70	10.8±1.48	11.4±1.43**

TP-*Thespesea populne*, values are expressed as mean±SEM, *p<0.01 compared with control group using one-way ANOVA followed by Dunnett's test.



TP-*Thespesea populne*

Figure 2: Percent increase in latency time of standard and test groups in comparison to control group for paw licking response in mice using hot plat method.

Acetic acid induced writhing test

Preclinical observations made in the form of numbers of writhing in 20 minutes using acetic acid induced writhing model are depicted in (Table 2). Percent increase in writhing inhibition in standard and test groups post treatment in comparison to the control group is depicted in (Table 2 and Figure 3). It was observed through the current study findings that pre-treatment with diclofenac (10mg/kg) and bark extract of *Thespesea populnea* (3/10/30 mg/kg) significantly inhibited acetic acid induced writhing behaviour in mice. It was observed that extract of *Thespesea populnea* produced dose dependent inhibition in writhing behaviour. The results suggests that extract of *Thespesea populnea* possess significant analgesic activity against acetic acid induced pain, however its potency was found to be lesser than diclofenac sodium.

Table 2: Number of writhing and percentage inhibition in writhing response observed in mice up to 20 minutes using acetic acid induced writhing model.

Treatment groups	Number of writhing (counts/20 minutes)	Percent inhibition
Control	69.5±6.75	--
Standard (Pentazocine; 25mg/kg)	13.33±2.24**	80.81
Test group 1 (TP bark extract, 3 mg/kg)	41.5±8.32**	40.29
Test group 2 (TP bark extract, 10 mg/kg)	33.83±4.17**	51.32
Test group 3 (TP bark extract, 30 mg/kg)	22.17±3.89**	68.10

Values are expressed as mean±SEM, **p<0.01 compared with control group using one way ANOVA followed by Dunnett's test.

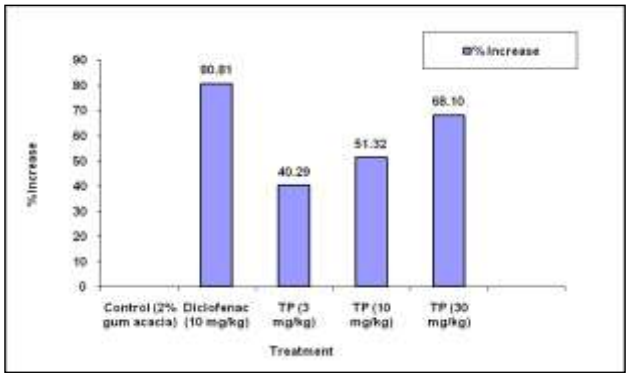


Figure 3: Percent inhibition in writhing response observed up to 20 minutes in standard and test groups compared to control group using acetic acid induced writhing model.

Formalin induced paw licking test

Preclinical observations made in the form of numbers of lickings made by mice in early phase (0-10 minutes) and late phase (20-30 minutes) using formalin induced paw

licking test are depicted in (Table 3). Percent increase in licking inhibition in both early and late phases in standard and test groups post treatment compared to the control group is depicted in (Figure 4-5).

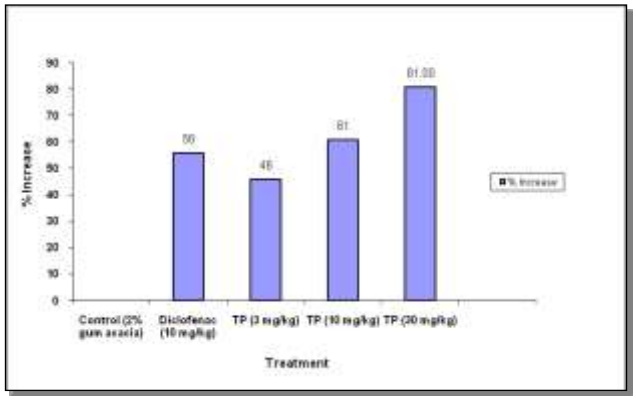


Figure 4: Early phase percent inhibition in licking response in standard and test groups compared to control group using formalin induced paw licking model.

Results of the current study findings depicted that pre-treatment with diclofenac (10 mg/kg) and bark extract of *Thespesea populnea* (3/10/30 mg/kg) significantly inhibited formalin induced paw licking behaviour in mice. It was observed that extract of *Thespesea populnea* produced dose dependent inhibition in paw licking behaviour. The results suggest that extract of *Thespesea populnea* possess significant analgesic activity against formalin induced pain in mice.

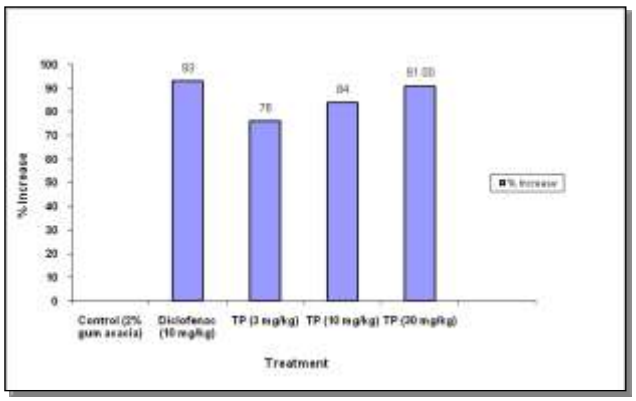


Figure 5: Late phase percent inhibition in licking response in standard and test groups compared to control group using formalin induced paw licking model.

Table 3: Number of paw lickings and percentage inhibition in licking response observed in treated mice using formalin induced paw licking model.

Treatment groups	Number of lickings		Percentage inhibition	
	Early phase (0-10 minutes)	Late phase (20-30 minutes)	Early phase (0-10 minutes)	Late phase (20-30 minutes)
Control	107±15.52	77.4±5.35	--	--
Standard (Pentazocine; 25mg/kg)	46.7±3.14**	4.67±0.67***	56.39	93.97
Test group 1 (TP bark extract, 3 mg/kg)	57.5±0.67***	18.5±1.45***	46.26	76.10
Test group 2 (TP bark extract, 10 mg/kg)	40.83±1.72***	12± 1.07***	61.84	84.50
Test group 3 (TP bark extract, 30 mg/kg)	19.67±1.38***	6.83± 1.14***	81.68	91.17

Values are expressed as mean±SEM, **p<0.01, ***p<0.001 compared with control group using one-way ANOVA followed by Dunnett's test

DISCUSSION

Results of current investigation revealed that bark extract of *Thespesea populnea* exhibited dose dependent analgesic activity, which was confirmed through preclinical hot plate induced paw withdrawal test model, acetic acid induced writhing test model and formalin induced paw licking test model. Observation made from hot plate induced paw withdrawal model revealed that no significant change in response of animals was observed over a period of three hours. The percent increase in reflex latency of the paw licking response in mice for standard drug pentazocin at a dose of 25mg/kg was observed to be at peak after 180 minutes. The intensity of analgesic activity of the *Thespesea populnea extract* was observed to be dose dependent. It is observed that the test drug at concentration of 10 mg/kg attained peak effect of 136% at 180 minutes, whereas standard drug pentazocine attained peak effect of 125% at 180 minutes. Observations thus revealed that bark extract of *Thespesea populnea* produced more analgesia compared to pentazocine. Since the classical hot plate model is reported to be suitable for measuring anti nociceptive effects of centrally acting analgesics, thus it can be conceived that analgesic effect of *Thespesea populnea* bark extract, is centrally acting.[28] Results of acetic acid induced writhing model revealed that in test group animals treated with *Thespesea populnea* bark extract number of writhings produced by acetic acid were significantly reduced by 40% at 3 mg/kg dose, 51% at

10mg/kg dose and 68% at 30 mg/kg dose compared to 80% reduction observed in 10 mg/kg of standard diclofenac solution. Acetic acid causes inflammatory pain by inducing capillary permeability and liberating endogenous substances that excite pain in nerve endings, NSAIDs inhibit cyclooxygenase in peripheral tissues and, therefore, interfere with the mechanism of transduction of primary afferent nociceptors.[29] Hence it can be perceived that *Thespesea populnea* bark extract may reduce writhing by inhibiting the release of endogenous substance, responsible for pain indicating that *Thespesea populnea* bark extract can also exhibit peripheral analgesic effect. Observations made from formalin induced paw licking model revealed that in early phase inflammatory pain (10 minutes immediately after the formalin injection) *Thespesea populnea* bark extract, at a dose of 30 mg/kg showed more efficacy compared to the standard drug diclofenac (10 mg/kg) in inhibiting the licking response, whereas in late phase (approximately 20 minutes after formalin injection) *Thespesea populnea* bark extract, at a dose of 30 mg/kg was observed to be almost equally effective (91%) compared to the standard drug diclofenac (93%) at a dose of 10 mg/kg. Pain in early phase is caused by C-fibre activation due to the peripheral stimulus inducing neurogenic pain. In late phase, pain appears to depend on the inflammatory reaction; in the peripheral tissue and functional changes in the dorsal horn of the spinal cord.[30] Thus the results indicated that *Thespesea populnea* bark extract can also inhibit supraspinal and spinal mediated neurogenic pain and peripherally mediated inflammatory pain.

Limitations

Limitations of current study were; the test substance in present investigation is from natural origin which is vastly biodiverse, this limitation can be addressed by standardization of the *Thespesea populnea* bark extract using officially reported techniques. The results and conclusion would have been more specific if the active constituent responsible for analgesic activity in *Thespesea populnea* bark extract could have been isolated and investigated.

CONCLUSION

It can be concluded from current study findings that *Thespesea populnea* bark extract exhibited good analgesic activity through all the three testing models. The extract at a dose of 10 mg/kg exhibited significant analgesia compared to the standard, pentazocine used in hot plate induced paw withdrawal model. The analgesic activity of extract was found to less compared to the standard, diclofenac sodium used in acetic acid induced writhing model, whereas in the early and late phase of formalin induced paw licking model, extract was observed to be having greater and equivalent analgesic response compared to diclofenac sodium respectively. Thus it can be overall concluded from the present the investigation that *Thespesea populnea* bark extract induces analgesia both peripherally and centrally and can inhibit supraspinal and spinal mediated neurogenic pain and peripherally mediated inflammatory pain.

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Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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