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ANTI-INFLAMMATORY AND ANALGESIC ACTIVITY OF ORAL DECOCTION OF *PTEROCARPUS SANTALINUS* BARK WOOD POWDER IN ACUTE INFLAMMATION MODEL

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ABSTRACT: Background: Raktachandan / *Pterocarpus santalinus* is mentioned to have edema reducing property in Ayurvedic literature. Studies have been performed using its methanolic extract for anti-inflammatory, analgesic and antioxidant activities. Since, Ayurveda advises to use it as a decoction, we planned to study the acute anti-inflammatory activity of decoction prepared from *Pterocarpus santalinus* bark-wood powder. **Methodology:** Albino rats of either sex were divided into 4 groups of 6 rats each (Group I – Control (CMC-vehicle), Group II – Ibuprofen suspension, Group III – *P. santalinus* suspension 3.5 mg/kg, Group IV – *P. santalinus* suspension 7 mg/kg. All the experimental animals were given standard and test drugs orally, 45 min before inducing inflammation. Acute inflammation was induced by injecting 0.1ml of 1% carrageenan solution in sub-plantar tissue of left hind paw of the rats. Paw volume (Plethysmometer) and pain assessment (Randall and Selitto paw withdrawal method) were done at 0 h (before medication), then at 1 h, 2 h, 3 h and 4 h after induction of inflammation. Data was analysed using Graph Pad Prism version 5. ANOVA followed by Tukey's test was used for comparison among groups. **Results:** *P. santalinus* suspension 7 mg/kg and ibuprofen treated rats showed significant reduction ($p<0.05$) in their paw volume compared to the other groups. There was significant reduction in pain threshold (gm/sec) in all the groups ($p<0.05$) but in *P. santalinus* 7 mg/kg and Ibuprofen treated groups the pain threshold gradually increased after 2 h of induction of inflammation. **Conclusion:** Orally given decoction of *Pterocarpus santalinus* bark-wood powder in 7 mg/kg dose showed significant anti-inflammatory and analgesic activity in carrageenan induced inflammatory model in rats.

INTRODUCTION: Inflammation is a localized protective response elicited by injury or destruction of tissues, which serves to destroy, dilute or wall off, both the injurious agent and the injurious tissue.

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Acute inflammation is characterised by sudden onset and marked by classical signs of heat, redness, swelling, pain and loss of function and in which vascular and exudative processes predominate.

Anti-inflammatory medications such as non-steroidal anti-inflammatory drugs (NSAID's) and glucocorticoids are widely used for the relief of symptoms in acute and chronic inflammatory conditions, but these are associated with common adverse effects such as gastric irritation and ulceration on long term use; whereas with steroid

use osteoporosis and infections are common and NSAIDs are associated with bleeding, hepato-toxicity, nephropathy.

Pterocarpus santalinus, also known as Red Sandalwood (English) and Raktachandan (Sanskrit), has a natural dye *i.e.* santalin, which is used as colouring agent in pharmaceutical preparations and foodstuffs. In the traditional system of medicine, the decoction from the wood is attributed various medicinal properties. It is known to have anti-hyperglycaemic activity, anti-pyretic, anti-inflammatory activities and also used as a cooling agent [1]. Hepatoprotective [2] and gastro-protective [3] properties of this natural medicine have also been proven.

Earlier studies on anti-inflammatory and analgesic activity of *P. santalinus*, were done using methanolic extract preparations orally in animal models of acute inflammation [4]. According to the clinical practices in Ayurveda, *P. santalinus* bark wood powder is used either topically as a paste, or its decoction (kadha) orally consumed in various ailments [5]. Recently, we had evaluated the activity of *P. santalinus*, topically in a chronic inflammatory model [6]. Therefore, an attempt was made here to study the anti-inflammatory and analgesic activity of oral *Pterocarpus santalinus* bark-wood powder as a decoction in an acute inflammatory model in rats.

MATERIAL AND METHODS: This study was conducted at the Department of Pharmacology, Bharati Vidyapeeth (Deemed to be University) Medical College, Pune, after getting approval from the Institutional Animal Ethics Committee (BVDUMC/2229/2017/ 001/002), according to the guidelines of the committee for the purpose of control and supervision of experiments on animals (CPCSEA).

Drugs and Chemicals: Carrageenan, *Pterocarpus santalinus* bark wood powder, carboxy methyl cellulose, ibuprofen syrup (Syp. Ibugesic - Cipla Ltd.)

Pterocarpus santalinus bark wood was purchased from the Ayurvedic medical store - Vaidya Khadiwale, and was authenticated at the Agharkar Research Institute, Pune by plant drug authentication service, botany group, plant sciences division (Voucher no. 55749), as authentication certificate Auth.15-072. The bark wood was dried, powdered and a decoction was prepared - where one part of the powder was added to 16 parts of distilled water and boiled till the solution reduced to half [7]. As per Ayurvedic literature, the human dose for *P. santalinus* is 80 ml (dwi-pala) per day of the decoction [8]. Two doses of the decoction were studied for the anti-inflammatory activity - 3.5 ml/kg and 7 ml/kg body weight of rat, after extrapolation from the human dose. These two doses were made into individual suspensions using 1% carboxy methyl cellulose as the decoctions were thick in consistency and difficult for oral administration in rats. Ibuprofen was purchased from the market in suspension form and administered at a dose of 100 mg/kg body weight orally to the rats [9].

Experimental Animals: 24 Albino rats of either sex, weighing 150 - 200 g each, were used for this study. These animals were housed in separate cages, fed with rat food pellets and water *ad libitum,* and cared for, as per CPCSEA guidelines. Animals were divided into four (4) groups having six (6) rats in each group, as follows:

Group I: Control (CMC-vehicle).
Group II: Ibuprofen suspension - 100 mg/kg.
Group III: *P. santalinus* suspension - 3.5 mg/kg.
Group IV: *P. santalinus* suspension - 7 mg/kg.

The standard and the test drugs were given orally to the rats. 45 min after administration of the drugs, acute inflammation was induced in these animals by injecting 0.1ml 1% carrageenan solution in the sub-plantar tissue of left hind paw of the rats [10].

Paw volume was measured hourly using a plethysmometer [11], where the inflammation induced paw of the animal was submerged in the water reservoir of the instrument, and the volume of water displaced was taken as the volume of the paw (measured in ml). This measurement was done at baseline (0 h) and repeated at 1 h, 2 h, 3 h and 4 h for all the animals in all the groups.

For assessment of pain, threshold for nociception was measured using the Randall and Selitto [12] paw withdrawal method, where a gradually increasing amount of pressure was applied on the inflammation induced paw using an Ugo Basile

Analgesy Meter. This measurement was done at baseline (0 h) and repeated at 1 h, 2 h, 3 h and 4 h for all the animals in all the groups. The pressure at which the animals withdrew their paws or squeaked was taken as the pain threshold of the rat (measured in grams per second).

Statistical Analysis: Data was presented as mean ± SEM. Data was analyzed by ANOVA followed by Tukey's test to compare values among groups using Graph Pad Prism version 5. P value <0.05 was considered statistically significant.

RESULTS: In this study, paw volume was measured using a Plethysmometer, after inducing acute inflammation in the left hind paws of all the animals. In the 1st h of induction of acute inflammation, there was increase in the mean paw volume in all the groups of animals which was significantly more in group III, while the mean paw volumes in the remaining groups (groups I, II and IV) were at par **Table 1**. At 2 h, paw volume in groups II and IV was significantly reduced as compared to group I, which subsequently kept reducing in the further hours, till the end of the experiment. At the end of the experiment (4 h), reduction in paw volume was maximum and at par in groups II and IV as compared to group I **Fig. 1**. In group III, reduction in paw volume was significantly evident only at 4 h as compared to group I (p<0.001).

TABLE 1: CHANGE IN PAW VOLUME OF THE STUDY GROUP ANIMALS (IN ml)

Time	Group I - Control (CMC-vehicle)	Group II - Ibuprofen Syrup	Group III - *P. santalinus* suspension - 3.5mg/kg	Group IV - *P. santalinus* suspension - 7 mg/kg
0 h	1.1 ± 0.035	1.2 ± 0.015	1.2 ± 0.033	1.2 ± 0.022
1 h	1.7 ± 0.013	1.7 ± 0.018	1.9 ± 0.046 ***	1.7 ± 0.071
2 h	1.8 ± 0.027	1.5 ± 0.031***	2.0 ± 0.045	1.5 ± 0.044***
3 h	1.9 ± 0.027	1.4 ± 0.023	1.8 ± 0.061	1.4 ± 0.050
4 h	2.0 ± 0.025	1.4 ± 0.030***	1.7 ± 0.070**	1.3 ± 0.036***

Values are expressed as mean ± SEM, ** p<0.001 and ***p<0.0001 as compared to Group I

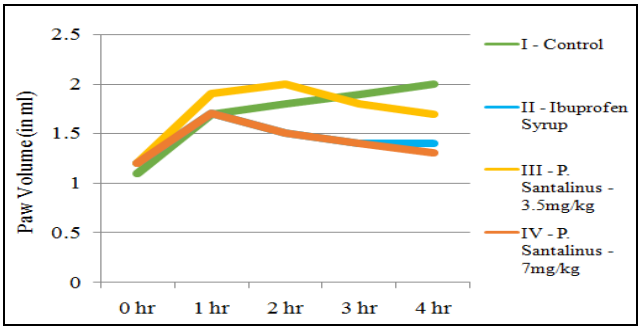

FIG. 1: CHANGES IN MEAN PAW VOLUME IN STUDY GROUP OF ANIMALS (0h - 4h)

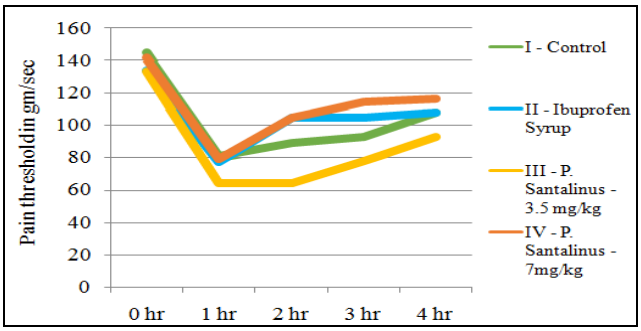

FIG. 2: CHANGES IN MEAN PAIN THRESHOLD IN STUDY GROUP ANIMALS (0h – 4h)

Pain threshold was measured using the Randall and Selitto paw withdrawal method which was seen to be decreased in all the study animals in the 1st h of induction of acute inflammation **Table 2** with statistically significant reduction in pain threshold in group III as compared to group I. This reduction in pain threshold in group III remained significantly low till the 3rd h of induction of inflammation, as compared to group I. The rise in pain threshold was statistically significant in group II at 2 h, and in group IV at 3 h of induction of inflammation as compared to group I **Fig. 2**.

TABLE 2: PAIN THRESHOLD OF THE STUDY GROUP ANIMALS (IN gm/sec)

Time	Group I - Control (CMC-vehicle)	Group II - Ibuprofen Syrup	Group III - *P. santalinus* suspension - 3.5mg/kg	Group IV - *P. santalinus* suspension - 7mg/kg
0 h	145 ± 5.1	134 ± 2.4	133 ± 3.7	142 ± 4.6
1 h	81 ± 6.1	77 ± 3.2	64 ± 2.4*	79 ± 3.9
2 h	89 ± 4.3	105 ± 3.9*	64 ± 2.3***	105 ± 5.6
3 h	93 ± 4.9	105 ± 3.1	78 ± 3.1*	115 ± 6.5*
4 h	108 ± 6.7	108 ± 3.5	93 ± 4.6	117 ± 5.9

Values are expressed as Mean ± SEM, * p<0.01 & ***p<0.0001 as compared to Group I

At the end of the experiment (4 h), increase in pain threshold was comparatively more in group IV as compared to group I and II, but it was not statistically significant. Rise in pain threshold is seen to be least in group III as compared to all the other groups, but it was not statistically significant.

DISCUSSION: Carrageenan induced local edema is a widely used model for neutrophil mediated acute inflammatory response. Earlier studies have shown that the cardinal signs of inflammation such as local swelling, erythema, hyperthermia and pain develop immediately following subcutaneous injection of carrageenan [13]. In this study too, paw volume was increased in all the animals within an hour of injection with carrageenan, denoting an acute localised inflammatory response. Ibuprofen is a non-steroidal anti-inflammatory drugs (NSAIDs) available for administration in various forms and is commonly used for acute and chronic, painful inflammatory conditions. In this study, we used a syrup preparation of ibuprofen as the standard drug for oral administration in rats. In this study, two oral doses of the *P. santalinus* decoction were assessed for their anti-inflammatory and analgesic activity, according to Ayurvedic literature. In previous studies, researchers have proven the anti-inflammatory and analgesic activity of *P. santalinus*, by using an alcoholic extract prepared from the bark wood powder [4]. We too assessed the same activity, but, using a decoction (kadha) prepared from the bark wood powder of *P. santalinus*, so as to mimic the clinical practices of Ayurveda.

Our study revealed that *P. santalinus* in the dose of 7 mg/kg, which was extrapolated from the human dose, showed significant reduction in inflammation as compared to the control group animals **Table 1**, **Fig. 1**. This anti-inflammatory effect seen with the study drug in the dose of 7 mg/kg was comparable to that seen with the standard drug ibuprofen. In the lower dose of 3.5 mg/kg, *P. santalinus* could show significant reduction in inflammation only at the end of the experiment *i.e.* at 4 h after induction of inflammation. This reduction in paw volume was quite less as compared to that seen in *P. santalinus* 7 mg/kg and ibuprofen group. Our observation regarding the effective anti-inflammatory dose of *P. santalinus* is at par with the one which is documented in Ayurvedic literature.

For studying the analgesic activity of the study drug *P. santalinus*, we observed the pain threshold in all the study groups (for 4 h) by the Randall & Selitto paw withdrawal method after induction of inflammation. Similar results were obtained as seen for the anti-inflammatory effect, that *P. santalinus* 7 mg/kg and ibuprofen group showed parallel efficacy in analgesic activity as compared to the control group which was statistically significant **Table 2, Fig. 2**. With the 3.5 mg/kg dose of *P. santalinus*, the pain threshold remained lower than all the other groups including the control group till the end of the experiment, depicting its inability to provide analgesia in this dose.

Ianaro has shown that intraplantar injection of carrageenan in mice produces tumor necrosis factor - α (TNF-α), interferon-γ andcytokines like interleukin-1 and 2, which induce nitric oxide synthase (NOS) in various cells. This inducible NOS along with the carrageenan induced cyclo-oxygenase contribute to the inflammatory response. Cho *et al*., had isolated two lignans from *P. santalinus* to study their biological properties and mechanism of action. Their study demonstrated that savinin, one of the lignan from *P. santalinus* inhibited TNF-*α* production and T cell proliferation and they suggested that this may act as the active principle for anti-inflammatory effect of the heartwood of *P. santalinus*.

Thus, our study demonstrates anti-inflammatory and analgesic activity of oral decoction of *P. santalinus* in the dose of 7 mg/kg in carrageenan induced acute inflammation. These activities of *P. santalinus* have been seen to be comparable to Ibuprofen which belongs to the preferred class of anti-inflammatory drugs, NSAIDs. Orally used NSAIDs are associated with a common adverse effect of gastric irritation. *P. santalinus* provides an added advantage over NSAIDs in this respect as it has been proven to be gastroprotective [3] in previous studies.

CONCLUSION: Oral decoction of *Pterocarpus santalinus* (7 mg/kg) bark wood powder has demonstrated significant anti-inflammatory and analgesic activity in rat model of acute inflammation which was comparable to standard drug ibuprofen.

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CONFLICT OF INTEREST: None declared.

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