Research Article

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COMPARATIVE ANTI-INFLAMMATORY STUDY ON THE EFFICACY OF LEAF AND ROOT OF AGNIMANTHA (*PREMNA CORYMBOSA* ROTTL.) IN WISTAR ALBINO RATS

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ABSTRACT

Agnimantha (*Premna corymbosa* Rottl.) belonging of Verbinaceae, is a small sized tree or large shrub which is grown throughout India. The used part, root is one among the Dasamoola (roots of 10 important plants) and Brhat panchamoola (roots of 5 important plant) and considered under Sothaharagana (group of drugs with anti-inflammatory action). Hence for therapeutic purposes, the entire plant is destroyed. If the same or more efficacy is obtained by its leaves than root or root bark, it will help in preservation of the plant as well as for the easy collection and administration. The study was done to evaluate and compare the *Sothagghna* Property (anti-inflammatory effect) of decoction of Patra (leaf) and Moola (root) of Agnimantha (*Premna corymbosa* Rottl.) on Wistar Albino rats. In vivo anti-inflammatory activity of the drugs was evaluated in Wistar albino rats using Carrageenan induced hind paw and cotton pellet implanted granuloma models. Experimental study rules out any significant difference between the two parts of the drugs in the dose of 8.64 ml/kg with respect to anti-inflammatory activity. Leaf of Agnimantha shows weak to moderate anti-inflammatory activity against acute inflammation at equivalent doses to root of Agnimantha. This provides preliminary evidence for carrying out further doses eliciting dose response pattern to ascertain whether higher doses of leaf produce good anti-inflammatory effect. If that is so it can be considered as possible substitute for root. Weight to weight basis it may not be an adequate substitute for the roots.

Keywords: Agnimantha, *Premna corymbosa* Rottl., Verbinaceae, Dasamoola, Brhat panchamoola, Sothahara, Anti-inflammatory

INTRODUCTION

Need for study: Majority of the formulations under Indian systems of medicine predominantly contain plant-based raw materials. For centuries, the forests have been the source of herbs and medicinal plants. The availability of medicinal plants collected from forests has become uncertain in the last few decades and as well as the demand for herbs and plants have been increasing due to increase in interest for use of herbal medicines.^{2,3} In this situation it's time to think of an alternative. In the formulations where the moola (root) are taken as the used part, there, it's being adulterated and substituted with other plants moolas (roots), so the effectiveness of that formulation is diminished and there by the believe in our system of medicine is affected. And if the moolas (roots) itself is taken, that particular plant is to be uprooted completely, which will lead to the death of that plant which was grown in many years with our efforts, so if the roots of that particular plant is replaced with any other part of that plant itself instead of other plant, may give the same effect or more effect than adverse effects, then it will help in preservation of that plant as well as it will help in the easy collection and administration.

The study was taken up on *Premna corymbosa* Rottl., the other variety commonly available in South India having properties similar to *Premna intergrifolia* Linn., the current name of *Brihat Agnimantha*.⁴ With this perspective, the work was carried out to assess the comparative anti-inflammatory effect of leaf and root

Kashaya (decoction) of Agnimantha (*Premna corymbosa* Rottl.) experimentally.

MATERIALS AND METHODS

Ethics: The Experiments were conducted with prior permission taken from Institutional Animal Ethics Committee (Approval No. SDMCAU | IAEC | 2014-15 DG – 12.)

Place of study: SDM Centre for Research in Ayurveda and Allied Sciences, Kuthpady, Udupi, Karnataka, India.

Animals: Twenty four Albino rats (*Rattus norvegicus*) of Wistar strains of either sex weighing between 150 to 250 g were obtained from animal house attached to department of Pharmacology, SDM Research Centre, Udupi. The animals were fed with normal rat diet which was purchased from Sai Durga Feed, Bangalore and water ad libitum was given throughout the study. The housing provided the following conditions like controlled lighting of 12:12h light and dark cycle, temperature of 25°C and relative humidity of approximately 50%.

Control and standard drug used: Distilled water was the control and the standard drug was tablet Diclofenac sodium of 50mg (Hi Media Laboratories Pvt. Limited, Mumbai; batch number RM 1576-100 G.). A homogeneous solution of the drug was prepared by adding 50mg of CMC (Carboxymethyl cellulose; batch number QF1Q610371 from Merck Specialities Private Limited, Mumbai.) and 10 ml of distilled water to it.

Test drug preparation: The root and leaf of the drug Agnimantha [*Premna corymbosa* Rottl.] were collected from the Garden of Shri Dharmasthala Manjunatheshwara College of Ayurveda and Hospital, Hassan and its genuinity was confirmed. The obtained leaves and roots were cut into pieces of variable length and diameter and were kept for drying under shade and sunlight respectively, were made into coarse powder form with the help of pulveriser at the Department of Rasashastra and Bhaishajya Kalpana, Shri Dharmasthala Manjunatheshwara College of Ayurveda and Hospital, Hassan. The kwatha (decoction) of the leaves and roots were prepared as per the classical reference.⁵

Dose fixation for the animals: The dose fixation for experimental animals was done referring to the standard table of Paget and Barnes (1964) formula involving body surface area ratio.⁶

Test groups: Human dose for kwatha (decoction) is 2 pala (96ml) i.e.; 96 ml; According to the standard formula⁶ it was calculated as 8.64 ml/kg

Standard group for acute inflammation: The standard drug selected for the study was tablet Diclofenac sodium of 50mg. A homogeneous solution of the drug was prepared by adding 50mg of CMC (Carboxymethyl cellulose) and 10 ml of distilled water to it. The standard dose of tablet Diclofenac sodium for rats was obtained⁶ and was expressed in terms of mg.

Standard group for chronic inflammation: The standard drug selected for the study was tablet Ibuprofen of 200mg (batch no.LOT36777D7). A homogeneous solution of the drug was prepared by adding 50mg of CMC (Carboxymethyl cellulose) and 10 ml of distilled water to it. The standard dose of tablet Ibuprofen for rats was obtained⁶ and was expressed in terms of mg.

Experimental design: Rats of either sex were divided into four groups of six animals each using simple randomization methods as shown in Table 1 and Table 2.

Route of administration: The test drugs were administered orally by using rat feeding tube fixed to syringe.

Evaluation of anti-inflammatory activity

Acute anti-inflammatory activity: The acute anti-inflammatory activity was evaluated by carrageenan induced hind paw oedema test in Wistar albino rats by method of Winter et al (1962) The group specific drugs were administered orally for seven consecutive days and on the 7th day, 1 hour after the drug administration, acute inflammation was produced by injecting 0.1 ml of 1% carrageenan solution into the sub plantar surface of rat's left hind paw after marking at the paws tibio-tarsal articulation and also after recording the initial or basal left hind paw volumes up to the tibio-tarsal articulation. 1 hour after inducing of inflammation, the paw volume up to the tibio-tarsal articulation was measured and continued for the next 3rd, 6th and the 24th hour using a Plethysmometer (PLM-01 PLUS Orchid Scientific).

$$\text{Percentage change in paw oedema} = \frac{V_c - V_t}{V_c} \times 100$$

Where, Vc is the paw volume of control group and Vt is the paw volume of test group.

Chronic anti-inflammatory activity: The effect of test drug on chronic anti-inflammatory activity was evaluated by using cotton pellet implanted granuloma formation in rats as per the method described by D'arcy et al (1960). The rats were anaesthetized under ketamine (80 mg/kg, i.p), its dorsum was shaved and swabbed with 70% (v/v) alcohol. Later a Mid-line incision of 1cm was made in the intra-scapular region and with the help of small blunt forceps; a small tunnel was made on either side of the incision. One sterile cotton pellet weighing 100 mg (prepared by rolling of a cotton piece of 100 mg and sterilised by autoclaving for 30 min under 15 lbs pressure) was inserted on each tunnel and the incision was closed with interrupted sutures. Group specific drugs were administered for seven consecutive days starting from the day of implantation. The rats anesthetized were sacrificed on 8th day, after collecting blood from the right eye's canthal region using a capillary glass tube which was sent for biochemical analysis, later; they were subjected to dissection for the collection of Spleen, Adrenal glands, Lymph nodes. Implanted cotton pellets were removed and cleaned of extraneous tissues, whose wet weight was taken, then they were dried by placing them in a hot air oven overnight at 80°C and then again dry weight was taken. The difference between the initial weight and the final weight of the pellet after drying was taken as the weight of granuloma tissue. The weights of Spleen, Adrenal glands, Lymph nodes were noted. The dissected organs were preserved in 10% formalin and sent for histopathological study.

Statistical analysis: The experimental data were expressed as mean $\pm$ SEM. The data obtained was analysed by using one way analysis of variance (ANNOVA) followed by Dunnett's 't' test for determining the level of significance of the observed effects. A 'p' value of less than 0.05 was considered statistically significant. Graph Pad In Stat-3 was used for statistical analysis of the generated data.

RESULTS

Acute Inflammation / Carrageen Induced Paw Odema

Data related to the effect of test drugs on percentage increase of carrageenan induced paw edema is shown in the Table 3.

Chronic Inflammation / Cotton Pellet

Data related to the effect of test drug on weight of cotton pellet has been shown in the Table 4.

Data related to the effect of test drug on weight of spleen, lymph node, Adrenal glands has been shown in the Table 5.

Histopathological Evaluation: Microscopic examination of tissue sections of different organs from different groups was carried out under various magnifications. It is shown in plates 1 to 3.

Biochemical Investigation: Serum C-reactive protein (CRP) was analyzed.

Data related to the effect of test drug on serum CRP level has been shown in the Table 6

Table 1: Acute inflammation – grouping of animals

Grouping	Study	Dosage
Group - 1 Control group	Distilled water was given	5ml/kg
Group - 2 Standard group	Diclofenac was administered	5mg/kg
Group - 3 Trial group	Patra Kvatha <i>Premna corymbosa</i> Rottl. was administered	8.64 ml/kg
Group - 4 Trial group	Moola Kvatha <i>Premna corymbosa</i> Rottl. was administered.	8.64 ml/kg

Table 2: Chronic inflammation – grouping of animals

Grouping	Study	Dosage
Group -1 Control group	Distilled water was given	5mg/kg
Group - 2 Standard group	Ibuprofen was administered.	5mg/kg
Group - 3 Trial group	Patra Kvatha of <i>Premna corymbosa</i> Rottl. was administered	8.64ml/kg
Group - 4 Trial group	Moola Kvatha of <i>Premna corymbosa</i> Rottl. was administered.	8.64ml/kg

Table 3: The effect of test drug on percentage inhibition of paw volume at different time interval

Group	Dose mg/ kg	Dosage form	Percentage increase of paw edema at different time interval		
			1 st H	3 rd H	6 th H
Control (normal tap water)	5ml/kg	Liquid	1.42 ± 0.05**	1.51 ± 0.06**	1.80 ± 0.11**
Standard (diclofenac sodium)	5ml/kg	Liquid	1.03 ± 0.03	1.10 ± 0.07**	0.93 ± 0.10
Test drug 1 <i>Agnimantha</i> leaf (<i>Premna corymbosa</i>)	8.64ml/kg	Patra kwatha	1.12 ± 0.05**	1.49 ± 0.07**	1.47 ± 0.06**
Test drug 2 <i>Agnimantha</i> root (<i>Premna corymbosa</i>)	8.64ml/kg	Moola kwatha	1.26 ± 0.04**	1.28 ± 0.03**	1.23 ± 0.01**

Data: MEAN ± SEM, **P<0.01, *P<0.05

Table 4: Effect of test drugs on cotton pellet implanted granuloma formation

Group	Dose mg/ kg	Dosage form	Granuloma tissue weight (mg)/100g body weight Mean ±SEM	% change
Control (normal tap water)	5ml/kg	Liquid	151.92 ± 15.61	
Standard (diclofenac sodium)	5ml/kg	Liquid	130.07 ± 20.18	14.38↓
Test drug 1 <i>Agnimantha</i> leaf (<i>Premna corymbosa</i>)	8.64ml/kg	Patra kwatha	166.24 ± 7.31	9.42↑
Test drug 2 <i>Agnimantha</i> root (<i>Premna corymbosa</i>)	8.64ml/kg	Moola kwatha	164.08 ± 12.19	8.00↑

Data: MEAN ± SEM

Table 5: Effect of test drugs on weight of Spleen, Lymph nodes and Adrenal gland

Group	Dose mg/ kg	Dosage form	Mean±SEM Spleen weight (g)	% change	Mean ± SEM Lymph nodes weight (g)	% change	Mean ± SEM Adrenal gland weight (g)	% change
Control (normal tap water)	5ml/kg	Liquid	0.94 ± 0.05		0.30 ± 0.05		0.07 ± 0.00	
Standard (diclofenac sodium)	5ml/kg	Liquid	1.12 ± 0.09*	28.72↑	0.22 ± 0.06	93.33↓	0.082 ± 0.01	14.63↓
Test drug 1 <i>Agnimantha</i> leaf (<i>Premna corymbosa</i>)	8.64ml/kg	Patra kwatha	0.95 ± 0.05	1.063↑	0.20 ± 0.02	33.33↓	0.06 ± 0.00	14.28↓
Test drug 2 <i>Agnimantha</i> root (<i>Premna corymbosa</i>)	8.64ml/kg	Moola kwatha	0.84 ± 0.05	10.63↓	0.22 ± 0.02	26.66↓	0.05 ± 0.00	28.57↓

Data: MEAN ± SEM, *P<0.05

Table 6: Effect of test drugs on serum C - reactive protein level in cotton pellet implanted rats

Group	Dose mg/ kg	Dosage form	Serum C - reactive protein (mg/dL) MEAN $\pm$ SEM	% change
Control (normal tap water)	5ml/kg	Liquid	0.78 $\pm$ 0.16	
Standard (diclofenac sodium)	5ml/kg	Liquid	1.28 $\pm$ 0.15	0.641 $\uparrow$
Test drug 1 <i>Agnimantha</i> leaf (<i>Premna corymbosa</i>)	8.64ml/kg	Patra kwatha	1.55 $\pm$ 0.20*	0.98 $\uparrow$
Test drug 2 <i>Agnimantha</i> root (<i>Premna corymbosa</i>)	8.64ml/kg	Moola kwatha	1.34 $\pm$ 0.19	0.717 $\uparrow$

Data: MEAN $\pm$ SEM, *P<0.05

1.1 Standard

1.2 Control

1.3 Test 1

1.4 Test 2

Plate 1: Showing microphotographs of Spleen of Control, Standrd and Test group 1 and 2

2.1 Standard

2.2 Control

2.3 Test 1

2.4 Test 2

Plate 2: Showing microphotographs of Lymph nodes of Control, Standard and Test group 1 and 2

3.1 Standard

3.2 Control

3.3 Test 1

3.4 Test 2

Plate 3: Showing microphotographs of Adrenal glands of Control, Standard and Test group 1 and 2

DISCUSSION

Agnimantha is the one drug among the Dasamoolas (roots of 10 important plants) and also one among the Brhat panchamoolas (roots of 5 important plant). According to Dhanwanthari nigantu, Tarkari, Nadeyi, Kshudra agnimantha⁴ are the synonyms mentioned for Agnimantha. Tarkari (*Clerodendrum phlomidis* Linn.) is having current name as *Clerodendrum multiflorum*, Nadeyi (*Premna integrifolia* Linn.) has current name as *Premna corymbosa* (syn- *Premna spinosa* Roxb) and Kshudra agnimantha (*Clerodendron inerme* Linn. Gaertn) is having current name as *Clerodendrum inerme* (Linn.f.) Gaertn⁴ and also in South India, especially in Kerala *Premna* sps. is used.⁷ It is used along with Shilajith in the treatment of

Obesity¹¹. Here the two parts of the drug Agnimantha (*Premna corymbosa* Rottl.) i.e.; the roots and leaves were evaluated for anti inflammatory activity using Carrageenan induced hind paw edema and Cotton pellet induced granuloma models.

Acute Inflammation: Carrageenan induced hind paw edema test is based on the principle of release of various inflammatory mediators by carrageenan.⁸ From the critical analysis of the result, administration of Agnimantha leaf and root kwatha (decoction) at the dose of /kg b.w orally showed moderate to significant decrease in the 1st hour, similar to the standard drug, diclofenac. While in the 3rd hour, the Agnimantha root group and the standard group showed moderate to significant decrease and the Agnimantha leaf group showed only mild non

significant decrease of paw volume. In the 6th hour all the 3 groups showed significant decrease in the paw volume but the difference is the standard group showed high significant decrease, and the Agnimantha leaf and root group showed only moderate decrease in paw volume. And in the 24th hour, the standard and the Agnimantha root group showed mild non significant decrease of paw volume and the Agnimantha leaf group showed moderate nonsignificant increase in paw volume.

Analysis of the activity profile shows that reference standard Diclofenac produced significant anti-inflammatory activity against carrageenan paw oedema up to 6 h after injection of the phlogistic agent confirming its potent anti-inflammatory activity. Significant inhibition up to 6 h was observed in Agnimantha root group also confirming presence of anti-inflammatory activity- however, the intensity of the observed effect was moderate to significant and less in comparison to Diclofenac group. In Agnimantha leaf group significant inhibition was observed at 1 h and 6 h while the oedema suppression observed at 3rd hour is weak and non-significant. This effect waned off by 24 th hour in all the groups- indicating transient nature of the activity observed.

The carrageenan paw oedema occurs in biphasic manner with different mediators involved in different phases of oedema formation. The initial phase is reported to be due to formation and release of inflammatory mediators like serotonin, bradykinins and the more pronounced later phase is mediated through release of prostaglandins. In Diclofenac and Agnimantha root groups' inhibition of the release or activity or both of the inflammatory mediators seems to be involved in the expression of anti-inflammatory activity. Agnimantha leaf activity is weak against first phase mediators and moderate against second phase mediators. The point to be noted here is presence of anti-inflammatory activity in Agnimantha leaf though of lower magnitude. This indicates requirement for dose response studies to ascertain whether using higher dose would have produced significant anti-inflammatory activity in all the phases. This can be resolved through further studies.

Chronic Inflammation: Cotton pellet implanted granuloma model is based on the foreign body granuloma that can provoke by subcutaneous implantation of pellets of compressed cotton in rats.⁹ From the critical analysis of the result, administration of Agnimantha leaf and root kwatha (decoction) showed mild nonsignificant increase in the cotton pellet granuloma whereas the standard group produced moderate but non-significant decrease in cotton pellet granuloma formation.

Administration of Agnimantha leaf and root kwatha (decoction) showed mild nonsignificant increase and mild nonsignificant decrease in the weight of spleen respectively. And while coming to the weight of adrenal gland the standard and the Agnimantha leaf group showed mild nonsignificant decrease, and the Agnimantha root group showed moderate nonsignificant decrease. On considering the weight of lymph nodes, the Agnimantha leaf and root group showed moderate nonsignificant decrease in the weight of Lymph nodes, while, standard group showed highly nonsignificant decrease for the same.

Agnimantha classical preparations have not been extensively evaluated against models of chronic inflammation. In the present study both Agnimantha leaf and root at the dose of 8.64ml/ kg in decoction form failed to suppress chronic inflammation in the form of granuloma formation. The drug in other form may be evaluated for this purpose. The present study clearly indicates in

the form used and the dose studied, Agnimantha is not effective against chronic inflammation.

Histopathological Evaluation: Histological examination of adrenal gland did not reveal any major difference among the groups indicating that adrenal stimulation is not one of the mechanism of action for the observed effect. Decreased cellularity was observed in lymph node in reference standard and Agnimantha leaf kwatha (decoction) treated group without any significant change in the cytoarchitecture of spleen. The decreased cellularity in lymph node may be indicative of suppression lymphoproliferation. This effect was not observed in Agnimantha root kwatha (decoction) group- indicating different mechanisms. Increase in the spleen weight in standard group may be indicative of immunomodulation effect.

Biochemical Evaluation: Serum C-reactive protein (CRP) is a specific abnormal protein that appears in the blood in response to inflammatory cytokines such as interleukin-6 (IL-6) during an inflammatory process. It is one of the most sensitive acute – phase reactants. CRP levels in the body have been used as a marker or indicator of inflammation.¹⁰ From the critical analysis of the results, the two parts of the drug Agnimantha (*Premna corymbosa* Rottl.) has shown increase in serum CRP level. However the root group showed better effect than leaves group

CONCLUSION

In carrageenan induced paw edema for acute inflammation, Agnimantha (*Premna corymbosa* Rottl.) leaves and root decoction at a dose of 8.64 ml/kg has shown significant suppression in odema up to 6 h confirming presence of anti-inflammatory activity- however, the intensity of the observed effect was moderate to significant and less in comparison to Diclofenac group. While in Agnimantha leaf group, the oedema suppression observed at 3rd hour is weak and non-significant. This effect waned off by 24 th hour in all the groups- indicating transient nature of the activity observed.

Agnimantha classical preparations have not been extensively evaluated against models of chronic inflammation. In the present study both Agnimantha leaf and root dose of 8.64 ml/kg in decoction form failed to suppress chronic inflammation in the form of granuloma formation.

Based on the data generated it can be suggested that leaf of Agnimantha shows weak to moderate anti-inflammatory activity against acute inflammation at equivalent doses to root of Agnimantha. This provides preliminary evidence for carrying out further doses eliciting dose response pattern to ascertain whether higher doses of leaf produce good anti-inflammatory effect. If that is so it can be considered as possible substitute for root. Weight to weight basis it may not be an adequate substitute for the roots.

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