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Research Article

Evaluation of anti-inflammatory activity of *Boswellia serrata* on carrageenan induced paw edema in albino Wistar rats

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ABSTRACT

Background: Inflammation is a response of the immune system, guarding the individual against infection. It is a major burning problem worldwide and billions of individuals are affected. Moreover administration of current anti-inflammatory drugs is often associated with severe side effects. Hence alternative therapeutic modules are necessitated. Now a day's herbal medicines are using due to their high efficacy and harmless to cure the diseases. In traditional medicine *Boswellia serrata* (*B. serrata*) has been widely used to treat various diseases which also include Inflammation. Till now the effect of B serrata on inflammation was not well understood. Hence In the present study we made an attempt to evaluate the anti-inflammatory activity of B. Serrata against carrageenan induced paw edema which is acute model of inflammation.
Methods: Albino wistar rats were divided into five groups, group 1 treated with carrageenan (control) whereas group 2, 3, and 4 treated with different doses (50, 100, and 200 mg/kg/bw) of *B. serrata* along with carrageenan, respectively. Group 5 treated with standard drug (Indomethacin 10 mg/kg/bw). Carrageenan induced paw edema and histopathological study of paw were evaluated in all experimental rats.
Results: The present study clearly demonstarted that carrageenan significantly increased paw edema and cellular infiltrates whereas *B. serrata* treated rats significantly decreased the paw edema and histopathological finding of cellular infiltrates and found to be greater at higher concentration i.e., 200 mg/kg/b/wt as compared to standard drug.
Conclusions: The findings from the above study proves that *B. serrata* has high anti-inflammatory activity and supports its usage in traditional medicine as herbal anti-inflammatory medicine.

Keywords: *B. serrata*, Anti-inflammation, Carrageenan, Paw histology

INTRODUCTION

Boswellia serrata is widely used in Ayurveda from ancient India. It is also referred as Indian Frankincense.[1] From centuries resin derived from it used to treat arthritis associated chronic inflammatory illnesses in Asian and African folk medicine.[2] The texts of Ayurveda and Unani cites that it is used as an effective remedy for treating diarrhoea, dysentery, ringworm, boils, fevers, skin and blood diseases, cardiovascular diseases, mouth sores, bad throat, bronchitis, asthma, cough, vaginal discharges, hair-loss, jaundice, hemorrhoids, syphilitic diseases, irregular menses and liver disorders. It also acts as diaphoretic, astringent, diuretic and acts both as internal and external stimulant.[3,4] Recent studies also states that it has anti-arthritic, anti-inflammatory, anti-hyperlipidemic, anti-atherosclerotic, analgesic and hepato-protective effect.[5]

Inflammation is an important physiological reaction which occurs in response to a wide variety of injurious agents such as physical trauma, bacterial infection,

chemicals or any other physical phenomenon ultimately aiming to perform the dual function of limiting the damage and promoting tissue repair.[6] The inflammatory process protects our body by releasing cells and mediators that combat foreign substances and prevent infection.[7-8]

Previous studies clearly demonstrated various efficient drug development strategies and drug targeting mechanisms based on in-silico drug designing, along with synthesis of novel therapeutic molecules for treating various diseases and disorders like cancer and diabetes along with inflammation.[9-13] However, inflammation still remains incurable. In cancers, the connectivity between inflammation and tumorigenesis is well-established and is supported by genetic, pharmacological, and epidemiological data.[14]

For instance, inflammatory bowel disease is an important risk factor for the development of colon cancer along with other genetic factors.[15-17] Similarly, recent advancements in modern clinical and surgical procedures like Appendicectomy for Acute Appendicitis and removal of malignant thyroid nodules.[18,19] Chetan also fail to relive from Inflammation related to various diseases and disorders.[20]

Non-steroidal anti-inflammatory drugs (NSAIDs) are a group of drugs commonly used to treat inflammation. NSAIDs block the production of PGs by inhibiting both COX-1 and COX-2. Most of these drugs are associated with well-known side effects at the gastrointestinal level and less frequently at the renal level.[21] Hence development of novel therapeutic agents against Inflammation is of paramount importance.

At present, the usage of medicinal plant/herbal medicine for treating various disorders and diseases is rapidly progressing.[22]

Moreover it is presumed to have no side effects. The active ingredients present in these Medicinal /herbal plants have been shown to efficiently slow down the disease symptoms in a synergistic manner.[23] The active ingredients of these plants may encompass polysaccharides, pigments, steroids, terpenoids, flavonoids and alkaloids.[24]

These Medicinal/herbal plant extracts and purified molecules have been demonstrated significant role in controlling various diseases and disorders. In spite of therapeutic potential of Medicinal plant/herbal plants, its effect on inflammation has not been studied in detail.

Moreover in Indian traditional medicine *B. serrata* has been employed in treating various ailments which include Inflammation. However studies related to its usage is still lacking. Therefore, we are interested in screening and evaluating the efficacy of *B. serrata* preparations against carrageenan induced paw edema in experimental rat models.

METHODS

Boswellia serrate: extract and dose preparation

Purified commercially available *B. serrata* plant extract was procured from INDFRAG Company, Bangalore, India and dissolved to desired concentration in normal saline.

Experimental animals

Healthy male albino wistar rats (180±20g) were procured from Sri Venkateswara Enterprises, Bangalore, Karnataka, India (Reg. No: 237/99/CPCSEA). Animals were maintained in the animal house of Sri Venkateswara University, Department of Zoology, Tirupati.

Rats were kept in sterilized polypropylene cages lined with paddy husk (18"x10"x8"). The animals were maintained under a regulated 12 h light: 12 h dark scheduled at 24±1^{o}C and relative humidity of 55±15%. Rats were provided standard rat chow (Sai Durga Feeds and Foods, Bangalore, India) and water *ad libitum*. Ethical clearance was obtained from the Institute animal Ethics Committee for handling the experimental animals.

Grouping of animals

Rats were randomly divided into five groups, each group consisting of six individuals and were named as follows:

Group-I: Carrageenan (1%) Induced Paw Edema
Group-II: Carrageenan + 50gm/kg/bw BS
Group-III: Carrageenan + 100mg/kg/bw BS
Group-IV: Carrageenan + 200mg/kg/bw BS
Group-V: Carrageenan + 10mg/kg/bw Indomethacin

Anti-inflammatory activity

Carrageenan induced paw edema

The anti-inflammatory activity of the *B. serrata* was determined by the method of Winter *et al.*[25] All group rats were injected with 1% Carrageenan (in 1% CMC) solution into the subplanter region of rat right hind paw. The first group referred as control received normal saline, whereas second, third and fourth groups received low dose (50 mg/kg/bw), mid dose (100 mg/kg/bw) and high dose (200 mg/kg/bw) of *B. serrata* through oral gavage respectively.

Fifth group served as standard, received Indomethacin (10 mg/kg/bw) through oral gavage. Before 1hour of injecting of Carrageenan the rats were treated with different doses of *B. serrata* and Indomethacin and normal saline.

The volume of paw edema was measured by dislocation of the water column in a Plethysmometer (UGO Basile, USA) immediately after Carrageenan injection at 0, 1, 2, 3, 4 and 5 hour.

The average paw volume was measured and compared with control and standard groups. Reduction in the paw volume in *B. serrata* pretreated groups compared with the control animals was considered as anti-inflammatory response.

The percentage of paw edema inhibition was calculated by using the following formula.[26]

Inhibition of Paw edema (%) = Oc - Ot / Oc X 100.

Where 'Oc' is edema volume of control group and 'Ot' is edema volume of treated groups.

Histopathological study

Paw region was collected from all the experimental rats after sacrificing through cervical dislocation. The specimens were fixed in neutralized formalin, dehydrated with ethanol and embedded in paraffin wax (56°C). Serial sections were taken and stained with haematoxylin and eosin.[27] The stained sections were observed under microscope and the histological changes were recorded with the help of a pathologist.

Statistical analysis

Statistical analysis of the data was performed with InStat statistics software. A p value of <0.05 was considered as statistically significant.

RESULTS

The anti-inflammatory effect of some of the medicinal plants/herbs have been validated and few others disproved.[28] However, traditional knowledge needs to be coupled with modern medicine and more scientific research needs to be done to verify the effectiveness, and elucidate the safety profile of such traditional/herbal remedies for their anti-inflammatory potential.

Therefore the present study is undertaken in an aim to screen the efficacy of anti-inflammatory potential of *B. serrata* in experimental rats. In the present study, the acute inflammation was experimentally induced by Carrageenan to determine the anti-inflammatory activity of *B. serrata* in rats.

After 1hour of oral administration of *B. serrata* at different doses (50, 100 and 200 mg/kg/bw) and Indomethacin (10 mg/kg/bw), The acute inflammation was induced by subplantar injection of 1% Carrageenan in the right hind paw of rats (Table 1 and Figure 2).

Table 1: Effect of *B. serrata* on carrageenan induced paw edema in rat.

Groups	Paw edema volume (ml)				
	1st Hour	2nd Hour	3rd Hour	4th Hour	5th Hour
Group-I (Carrageenan)	1.74±0.04	1.79±0.08	1.82±0.082	1.86±0.054	1.89±0.071
Group-II (BS 50mg/kg/bw)	1.68±0.10	1.59*±0.06	1.67*±0.089	1.46*±0.11	1.43*±0.081
Group-III (BS 100mg/kg/bw)	1.64±0.05	1.45*±0.06	1.52*±0.06	1.44*±0.18	1.4*±0.02
Group-IV (BS 200mg/kg/bw)	1.51*±0.09	1.41*±0.04	1.47*±0.066	1.37*±0.22	1.21*±0.12
Group-V (Indomethacin (10mg/kg/bw)	1.56*±0.06	1.42*±0.05	1.53*±0.07	1.46*±0.07	1.30*±0.10

Values are mean±S.D. of 6 individual rats; *Values are significant at P<0.05 over control.

Table 2: Inhibition of paw edema in *B. serrata* and Carrageenan treated rats.

Groups	% of Inhibition of paw edema				
	1st Hour	2nd Hour	3rd Hour	4th Hour	5th Hour
Group-II (BS 50mg/kg/bw)	3.44	11.17	8.24	21.5	24.33
Group-III (BS 100mg/kg/bw)	5.74	18.99	16.48	22.58	25.92
Group-IV (BS 200mg/kg/bw)	13.21	21.22	19.23	26.34	35.97
Group-V Indomethacin (10mg/kg/bw)	10.34	20.6	15.93	21.5	31.21

Values are % of inhibition over control (Group-I).

After Carrageenan injection the rat paw edema volume was measured every one hour (upto 5h) in all experimental rats. The paw edema volume was increasing with every hour and observed volume was higher at 5th hour (Figure 1).

The different doses of *B. serrata* and Indomethacin treated rats showed an inhibition of Carrageenan induced paw edema in all observed time intervals as compared to Carrageenan induced paw edema. The inhibition of paw edema was observed greater in rats treated with *B. serrata* at high dose (35.97%) followed by Indomethacin (31.21%), mid dose (25.92%) and low (24.33%) at 5th hour observation (Table 2 and Figure 3).

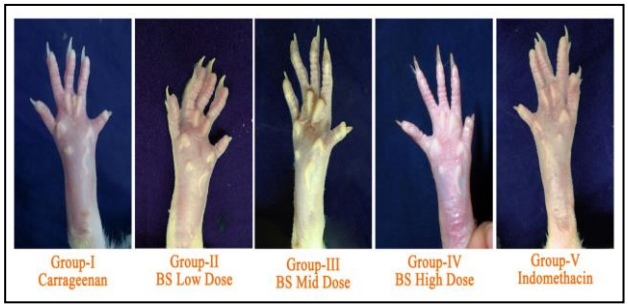
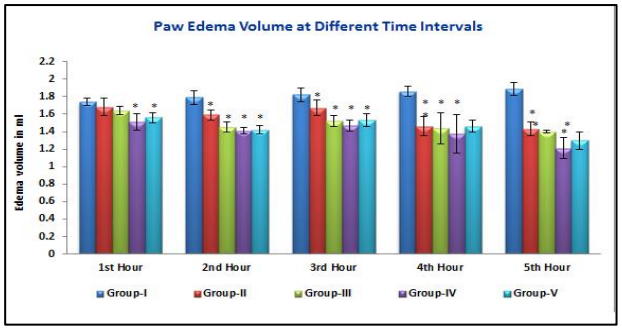
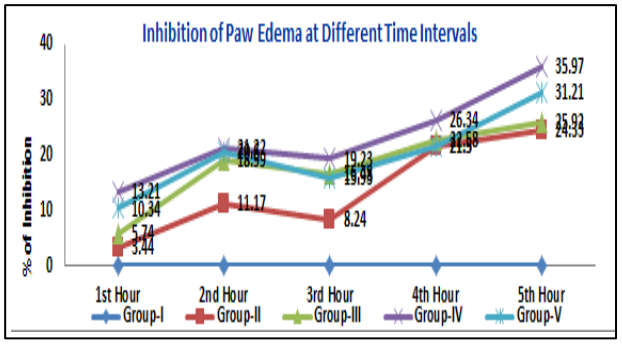


Figure 1: The anti-inflammatory activity of *B. serrata* was evaluated in Carrageenan induced paw edema.



* Values are significantly at P<0.05 over control.

Figure 2: Paw edema volume of *B. serrata* and carrageenan treated rats.



Values are % of inhibition over control.

Figure 3: Inhibition of paw edema volume in B. serrata and carrageenan treated rats.

Histopathological study revealed that sub-plantar injection of carrageenan lead higher cellular infiltrates whereas *B. serrata* and Indomethacin treated rats showed less cellular infiltrates as compared to carrageenan treated rats.

At higher concentration of B. serrata treated rats showed greater effect in reducing the cellular infiltrates as compared with standard drug (Figure 4).

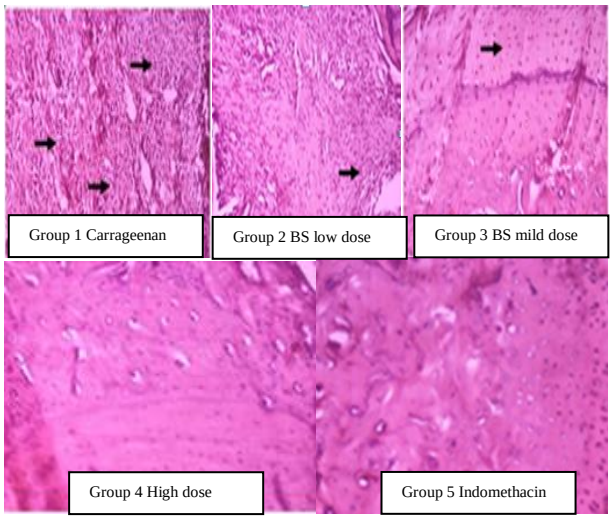


Figure 4: Histological changes in paw edema after injection of carrageenan and *B. serrata* treated rats with 10x magnification. Arrows indicates the infiltrated cells.

DISCUSSION

The administration of current anti-inflammatory drugs is often associated with severe side effects. Hence alternative therapeutic modules are necessitated.[28] For the past few decades, the world population up to 75 to 80% relies on herbal medicines, for primary health care especially in developing countries, because of their better acceptability with human body and lesser side effects.[22-24] Few investigations have been initiated around the globe into researching, screening and analyzing the local plants with anti-inflammatory values.

The anti- anti-inflammatory effects of some of the medicinal plants have been validated and others disproved.[28] However, In spite of therapeutic potential of *B. serrata*, its effect on inflammation has not been studied in detail. Therefore, in the present study we screened and identified theanti-inflammatory efficacy of *B. serrata* preparations against carrageenan induced paw edema in experimental rat models.

As evidenced by earlier studies Induction of inflammation in experimental animal models is a huge task. Most studies revealed that so many factors play a role for the lack of uniformity in the induction of inflammation. Moreover the acute model of inflammation

is suited to evaluate the preventive effects of drugs while the delayed, chronic model is better adapted for studies on healing or resolution of inflammation. Carrageenan induced paw edema was commonly employed experimental acute model for evaluating the anti-inflammatory activity of natural compounds.[29] The results of the present study showed that, Carrageenan injection induced the paw edema volume and observed edema volume was higher at 5th hour.

Different doses of *B. serrata* and Indomethacin pretreated rats showed an inhibition of Carrageenan induced paw edema in all observed time intervals. At high concentration of *B. serrata* treated rats showed greater decreased in Carrageenan induced edema as compared with standard drug (Indomethacin), low and mid doses of *B. serrata*.

In histopathalogical study, we observed subplantar injection of Carrageenan induced inflammation in the form of accumulation of inflammatory cells like neutrophils whereas *B. serrata* treated rats decreased the cellular infiltrates at different concentrations and found to be greater in higher concentrations.

The development of carrageenan-induced edema is a biphasic event. The initial phase (0-1 h) is attributed to the release of serotonin, histamine, bradykinin and substance P. The late phase (after 1h) is mainly due to the neutrophil infiltration into the inflammatory site and the production of large amounts of pro-inflammatory mediators such as PGE2 and various cytokines such as IL-1β, IL-6, IL-10 and TNF-α.[30-32]

TNF-α is produced mainly by mononuclear phagocytes and can cause immune responses by stimulating macrophages and T cells. TNF-α can also induce secretion of other inflammatory cytokines.[33] Nuclear transcription factor-kappa B (NF-κB) and mitogen-activated protein kinase (MAPK) signal pathways are two important signalling pathways involved in inflammation response.[34]

NF-κB is an important transcription factor and activated NF-κB up-regulates the expression of proinflammatory cytokine genes, such as IL-1β, IL-6 and TNF-α.[35]

The classical MAPKs are comprised with three family members: c-Jun NH2-terminal kinase (JNK), mitogen-activated protein kinase (p38-MAPK) and extracellular signal-regulated kinase p42/p44 (ERK1/2), Davis.[36] Phosphorylation of MAPKs can promote the production of pro-inflammatory cytokines.[37-38]

The *B. serrata* inhibited the edema during acute phase of inflammation probably by inhibiting the chemical mediators of inflammation. The anti-inflammatory mechanism of *B. serrata* is through the inhibition of the leukotrienes synthesis[39].

In vitro anti-inflammatory testing by Viswanad Vidya *et al.*, revealed boswellic acids in blocking the inflammatory mediators, thereby reduces the inflammation.[40]

CONCLUSION

The carrageenan induced paw edema was commonly employed experimental acute model for evaluating the anti-inflammatory activity of natural compounds.[29]

The results of the present study showed that, carrageenan injection induced the paw edema and cellular infiltrates. Treatment of *B. serrata* inhibited the edema and decreases the cellular infiltrates probably by inhibiting the inflammatory mediators. From the results it is proved that *B. serrata* has high anti-inflammatory activity and suggests as herbal anti-inflammatory medicine.

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