



***Boswellia serrata* normalizes altered haematological indices, attenuates pain and inflammation associated with adjuvant induced arthritis in rats**

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ABSTRACT

A study was carried out to evaluate the anti-arthritic potential of *Boswellia serrata* on haematological parameters, pain and inflammation associated with adjuvant induced rheumatoid arthritis in rats. Thirty male *Wistar* rats were randomly divided into 5 groups. While Group 1 served as normal control, Group 2 served as arthritic control, Groups 3, 4 and 5 served as treatment groups. Arthritis was induced in animals from Groups 2 to 5 with 0.1 ml of Freund's complete adjuvant injected intradermally into the foot pad of hindlimbs. Consequently, the onset of rheumatoid arthritis was indicated by hyperalgesia and inflammatory signs which were assessed by paw volume, paw diameter and paw withdrawal latency. Treatment protocol was followed from 3rd to 21st day, with *Boswellia serrata* given orally as methanolic extract at 500 mg/kg b.wt. to Group 3, meloxicam given subcutaneously at 1 mg/kg b.wt to Group 4 and both the drugs given concurrently to Group 5. The drug effects were evaluated on paw parameters and haematological indicators to depict the extent of paw inflammation and its subsequent amelioration. Conclusively, a major curative effect was witnessed with *Boswellia serrata* when compared to meloxicam.

Keywords: Adjuvant arthritis, *Boswellia serrata*, Inflammation, Haematology, Pain

Rheumatoid arthritis (RA) is a systemic autoimmune disease with a worldwide prevalence of 1% and approximately 0.75% in India (Rajendra *et al.* 2019). It leads to an inflammatory poly-arthritis characteristically described by a symmetrical pattern of the affected joints, morning stiffness, joint swelling and tenderness (Bendele 2001). The pathogenesis of RA involves communication between various inflammatory cells, particularly the macrophages, T lymphocytes and resident cells of the joints, via a network of proteins called cytokines. A wide range of cellular and humoral events together contribute to the pathology of RA (Cho *et al.* 2002, Mishafiey *et al.* 2005). Oxidative stress is an important mechanism that underlies the destructive proliferative synovitis. One of the most common causes for local bone erosion is the process of destruction of the juxta-articular bone in addition to which mild cartilage destruction also occurs (McInnes and Schett 2007).

Currently, the therapy for RA includes non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids, disease-modifying anti-rheumatic drugs (DMARDs) and some recently developed biological agents, all of which are associated with severe adverse effects. Many herbal drugs have long been reported to possess anti-inflammatory and anti-arthritic properties. Hence, this study was undertaken to evaluate the anti-arthritic potential of *Boswellia serrata*

on haematological parameters, pain and inflammation associated with adjuvant induced arthritis.

MATERIALS AND METHODS

The present study was conducted at the Department of Veterinary Pharmacology and Toxicology, College of Veterinary Science, Hyderabad. All the experimental procedures were duly approved by the Institutional Animal Ethics Committee.

Animals: A total of 30 male *Wistar* rats of same age, weighing 150–200 g procured from Sanzyme Laboratories, Hyderabad were used in the 21-day study. All the rats were housed in polypropylene cages and provided with *ad lib.* water and feed throughout the experiment. A 12 h light/dark cycle was maintained with all the rats acclimatized for a week before commencing the experiment.

Plant extract: A methanolic extract was prepared with dry resin powder of *Boswellia serrata* procured from Derex Laboratories, Hyderabad. Dry resin (100 g) was macerated with 200 ml of methanol for 72 h. The acquired solvent was filtered and evaporated until a semi-solid, viscous, brown mass was formed. This crude methanolic extract was dried, powdered and stored at 4°C until further dosing.

Experimental design: The rats were randomly divided into five groups, each containing six rats and were maintained for 21 days till completion of the study. Rheumatoid arthritis (RA) was induced with Freund's complete adjuvant (FCA) obtained from M/s Veterinary

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Biological Research Institute, Hyderabad. On '0th' day, all the animals except those from Group 1 were injected intradermally with FCA, onto the left hind foot pad. The treatment schedule followed for different groups of rats is as follows: Group 1, normal control; Group 2, adjuvant induced arthritic control; Group 3, treated with Meloxicam (MELONEX, Intas Pharma) @ 1 mg/kg bw subcutaneously; Group 4, treated with *Boswellia serrata* @ 500 mg/kg body weight orally; Group 5, treated with Meloxicam + *Boswellia serrata* extract.

Evaluation of paw inflammation: The progression of RA was evaluated weekly on 0th, 7th, 14th and 21st days. Paw volumes, paw diameter and paw withdrawal latency were measured using the digital plethysmometer (UGO BASILE 7140, Italy) (Milanino 1988), digital caliper (Barbier *et al.* 1984) and analgesiometer (Anderson *et al.* 1996), respectively. Based on Pavai *et al.* (2009) mobility score criteria (6, rat walks normally; 5, ipsilateral hindpaw touches fully on the floor; 4, only the toe of ipsilateral hindpaw touches the floor; 3, contralateral hindpaw touches fully on the floor; 2, only the toe of contralateral hindpaw touches the floor; 1, crawling using only fore paws; 0, rat does not move) and Butler *et al.* (1991) arthritic score criteria (0, normal paw; 1, mild swelling and erythema of digits; 2, moderate swelling and erythema of digits; 3, severe swelling and erythema of digits; 4, gross deformity and inability to use the limb), an average scoring was done to classify the extent of arthritis at the affected joints.

Haematological assessment: Whole blood was collected at weekly intervals for assessing haematological parameters such as red blood cell (RBC) count, white blood cell (WBC) count, haemoglobin (Hb) concentration, erythrocyte sedimentation rate (ESR) and packed cell volume (PCV). Prior to blood collection, feed was withdrawn for 12 h and the blood was collected through retro-orbital plexus under ketamine/xylazine anaesthesia. All the blood parameters were assessed in a blood analyzer.

Statistical analysis: The data were analysed statistically by applying one-way analysis of variance (ANOVA) using statistical package for social sciences (SPSS) version 17.0. Difference between the means were tested using Duncan's multiple comparison test and the significance level was set at $P < 0.05$.

RESULTS AND DISCUSSION

Rheumatoid arthritis (RA) is an autoimmune disease characterized by symmetric, erosive synovitis manifested extra-articularly (Harris 1990). Regardless of therapy, it presents a chronic fluctuating course resulting in progressive joint destruction, deformity and disability. In this study, the efficacy of *Boswellia serrata* was evaluated for its ameliorative potential against adjuvant induced rheumatoid arthritis.

The average weekly paw volumes (ml), paw diameter (mm) and paw withdrawal latency (sec) remained significantly increased in Group 2 arthritic rats throughout the experiment (Table 1). A notable decrease in the paw

inflammatory parameters was evident in treatment groups with Group 4 showing a better effect than Group 3 and, Group 5 showing an enhanced curative effect than Groups 3 and 4.

Paw volume assessment is a guide to evaluate the progression of arthritis following FCA administration. In this study, the arthritic rats showed increased paw volumes than the other groups, while treatment groups revealed significant reduction (Table 1). Increase in paw volumes could be due to prostaglandin E₂ (PGE₂), a powerful mediator synthesized in the joints (McCoy *et al.* 2002). Along with other inflammatory vasodilators such as histamine and bradykinin, PGE₂ contributes to erythema which increases blood flow to areas of acute inflammation (Patil *et al.* 2012). Reduction in paw volumes has been accredited to the anti-inflammatory property of *Boswellia serrata* (Kimmatkar *et al.* 2003). It is speculated that NSAIDs elicit their anti-RA effects by blocking the production of PGE₂ through inhibition of cyclooxygenases (COX) and prostaglandin synthase (Fahmi 2004), thereby reducing the exudate volume and migration of leukocytes to the site of inflammation.

Paw oedema, which relates to increased thickness of the foot, develops due to infiltration of inflammatory exudates and release of serotonin, histamine, bradykinin and leukotrienes from blood-derived cells such as eosinophils, neutrophils, macrophages and dendritic cells during the acute phase of the disease. Large amounts of pro-inflammatory mediators such as PGE₂ and various cytokines such as TNF- α , IL-1 β , IL-6 and IL-10 are also produced at the site of inflammation (Santos *et al.* 2012, Sadeghi *et al.* 2013). In this study, the reduction of paw diameter in treated groups (Table 1) may be attributed to either the inhibitory effect of meloxicam on cyclooxygenase-2 (COX-2) that induces inflammatory prostaglandins (Engelhardt *et al.* 1995) or the inhibition of leukotriene synthesis by Boswellic acids as reported earlier by Gayathri *et al.* (2007), Vidya *et al.* (2014) and Shaik *et al.* (2016).

Paw withdrawal latency measures the response to brief noxious stimuli which closely resembles clinical pain. Here, the treated groups showed better paw withdrawal latency (Table 1) suggesting anti-nociceptive effects of *Boswellia serrata* fractions as reported similarly by Sharma *et al.* (2010) and Sarvesh *et al.* (2019).

Arthritic scores and mobility scores are the indices of joint inflammation and disease development, respectively. In this study, the arthritic rats showed an increase in the arthritic score (0th day, 0 ± 0 ; 21st day, 4 ± 0^{aA}) and a decrease in the mobility score (0th day, 6 ± 0^{aA} ; 21st day, 0.67 ± 0.21^{dC}) while the treatment groups showed increased mobility scores (Group 3: 7th day: 3.5 ± 0.22^{cB} , 21st day: 4.5 ± 0.34^{bB} ; Group 4: 7th day: 3.67 ± 0.21^{cB} , 21st day: 4.67 ± 0.33^{bB} ; Group 5: 7th day: 3.67 ± 0.21^{cB} , 21st day: 4.83 ± 0.16^{bB}) and decreased arthritic scores (Group 3: 7th day: 2.43 ± 0.21^{aB} , 21st day: 1.17 ± 0.4^{bB} ; Group 4: 7th day: 2.33 ± 0.21^{aB} , 21st day: 1.15 ± 0.4^{bB} and Group 5: 7th day: 2.19 ± 0.16^{aB} , 21st day: 1 ± 0^{bB}). This may be due to the relative immobility

Table 1. Average weekly paw volume (ml), paw diameter (mm) and paw withdrawal latency (sec) of rats

Group	Paw volume (ml)				Paw diameter (mm)				Paw withdrawal latency (sec)			
	0 th day	7 th day	14 th day	21 st day	0 th day	7 th day	14 th day	21 st day	0 th day	7 th day	14 th day	21 st day
Control	1.01±0.04 ^{bbc}	1.1±0.03 ^{abd}	1.13±0.03 ^{abd}	1±0.01 ^{bc}	3.71±0.05 ^{ua}	3.22±0.05 ^{bc}	3.2±0.06 ^{bd}	3.2±0.5 ^{bd}	12.83±0.7 ^{ua}	12.67±1.02 ^{ua}	12.67±1.02 ^{ua}	12.83±0.7 ^{ua}
Arthritic control	1.13±0.03 ^{cab}	2.13±0.11 ^{ba}	2.37±0.08 ^{aba}	2.51±0.07 ^{ua}	3.74±0.1 ^{ca}	4.88±0.18 ^{ba}	5.02±0.1 ^{ba}	5.67±0.11 ^{ua}	13±0.93 ^{ua}	6±0.57 ^{bc}	5.67±0.33 ^{bc}	3.5±0.42 ^d
Meloxicam	1±0.01 ^{bc}	1.9±0.1 ^{ab}	1.8±0.08 ^{ab}	1.7±0.05 ^{ab}	3.64±0.05 ^{ba}	4.76±0.12 ^{ua}	4.74±0.13 ^{ab}	4.52±0.15 ^{ab}	12.67±1.02 ^{ua}	7.08±0.45 ^{bbc}	7.25±0.35 ^{bbc}	7.33±0.61 ^{bc}
<i>Boswellia serrata</i> (BS)	1.14±0.06 ^{ba}	1.71±0.03 ^{ab}	1.61±0.1 ^{ab}	1.51±0.08 ^{ac}	3.56±0.07 ^{ba}	4.7±0.12 ^{ua}	4.65±0.14 ^{ab}	4.38±0.6 ^{ab}	13.17±0.79 ^{ua}	7.17±0.4 ^{bbc}	7.42±0.55 ^{bbc}	7.42±0.55 ^{bc}
Meloxicam + BS	1.15±0.02 ^{ca}	1.47±0.02 ^{ac}	1.37±0.03 ^{abc}	1.26±0.07 ^{bcd}	3.73±0.05 ^{ba}	4.3±0.11 ^{ab}	4.3±0.04 ^{ac}	3.94±0.18 ^{bc}	12.83±0.94 ^{ua}	8.42±0.35 ^{bb}	8.67±0.38 ^{bb}	9.25±0.44 ^{bb}

Values are mean±standard error (n=6); One-way ANOVA; Means with different alphabets as superscripts differ significantly (P<0.05); Capital alphabets for vertical comparison and small alphabets for horizontal comparison.

Table 2. Average weekly RBC count, weekly WBC count and haemoglobin concentration of rats

Group	RBC count (×10 ⁶ /mm ³)				WBC count (×10 ³ /mm ³)				Haemoglobin concentration (g/dl)			
	0 th day	7 th day	14 th day	21 st day	0 th day	7 th day	14 th day	21 st day	0 th day	7 th day	14 th day	21 st day
Control	8.25±0.2 ^{ua}	8.24±0.2 ^{ua}	8.25±0.28 ^{ua}	8.25±0.27 ^{ua}	7.9±0.3 ^{ua}	7.91±0.22 ^{ac}	8.02±0.19 ^{ad}	8.02±0.19 ^{ad}	15.85±0.17 ^{ua}	15.83±0.17 ^{ua}	15.83±0.17 ^{ua}	15.8±0.25 ^{ua}
Arthritic control	8.23±0.28 ^{ua}	5.9±0.34 ^{bb}	5.61±0.19 ^{bd}	5.52±0.1 ^{bc}	8.02±0.19 ^{da}	14.2±0.4 ^{ca}	18.46±0.6 ^{ba}	23.84±0.5 ^{ua}	15.77±0.26 ^{ua}	9.97±0.5 ^{bc}	10.08±0.17 ^{bc}	8.58±0.13 ^{cd}
Meloxicam	8.25±0.31 ^{ua}	6.21±0.14 ^{bb}	6.23±0.15 ^{bc}	6.25±0.15 ^{bc}	7.89±0.18 ^{ba}	12.77±0.8 ^{ua}	12.56±0.61 ^{ab}	11.88±0.7 ^{ab}	15.8±0.25 ^{ua}	10.53±0.62 ^{bc}	10.58±0.54 ^{bc}	11.02±0.39 ^{bc}
<i>Boswellia serrata</i> (BS)	8.24±0.33 ^{ua}	6.5±0.11 ^{bb}	6.45±0.11 ^{bc}	6.62±0.14 ^{bb}	8.08±0.47 ^{ba}	12.56±0.61 ^{ua}	12.23±0.87 ^{ab}	11.75±0.62 ^{ab}	15.73±0.22 ^{ua}	10.55±0.53 ^{bc}	10.63±0.75 ^{bc}	11.37±0.36 ^{bc}
Meloxicam + BS	8.27±0.28 ^{ua}	7.59±0.15 ^{ba}	7.6±0.12 ^{bb}	7.77±0.16 ^{aba}	7.91±0.22 ^{ba}	10.92±0.47 ^{ab}	10.35±0.48 ^{ac}	9.97±0.78 ^{ac}	15.75±0.2 ^{ua}	12.11±0.33 ^{bb}	12.55±1.03 ^{bb}	12.77±0.63 ^{bb}

Values are mean±standard error (n=6); One-way ANOVA; Means with different alphabets as superscripts differ significantly (P<0.05); Capital alphabets for vertical comparison and small alphabets for horizontal comparison.

Table 3. Average weekly packed cell volume (%) and erythrocyte sedimentation rate (mm/h)

Group	PCV (%)				ESR (mm/hr)			
	0 day	7 th day	14 th day	28 th day	0 day	7 th day	14 th day	28 th day
Control	35.02±0.54 ^{ua}	35.03±1.06 ^{ua}	35.03±1.1 ^{ua}	35.03±0.55 ^{ua}	1.13±0.04 ^{ua}	1.13±0.04 ^{ac}	1.13±0.04 ^{ad}	1.13±0.04 ^{ad}
Arthritic control	35.05±1.1 ^{ua}	24.06±0.87 ^{bc}	22.72±0.62 ^{bd}	18.91±0.58 ^{cd}	1.13±0.04 ^{ca}	6.1±0.16 ^{ba}	6.25±0.07 ^{ba}	6.55±0.13 ^{ua}
Meloxicam	35.07±0.96 ^{ua}	24.96±0.28 ^{bc}	25.09±0.04 ^{bc}	26.25±0.61 ^{bc}	1.15±0.05 ^{ba}	5.85±0.26 ^{ua}	5.58±0.26 ^{ab}	5.24±0.35 ^{ab}
<i>Boswellia serrata</i> (BS)	35.03±1.06 ^{ua}	25.11±0.07 ^{cc}	26.47±0.45 ^{bcc}	27.63±0.61 ^{bc}	1.14±0.04 ^{ba}	5.61±0.28 ^{ua}	5.29±0.37 ^{ab}	4.87±0.44 ^{ab}
Meloxicam + BS	35.07±1.01 ^{ua}	27.63±0.61 ^{cb}	29.24±0.59 ^{cb}	31.88±0.19 ^{bb}	1.11±0.02 ^{ca}	4.58±0.32 ^{ab}	4.25±0.13 ^{ac}	3.02±0.01 ^{bc}

Values are mean±standard error (n=6); One-way ANOVA; Means with different alphabets as superscripts differ significantly (P<0.05); Capital alphabets for vertical comparison and small alphabets for horizontal comparison.

that resulted from severe paw swelling and oedema of peri-articular tissues. Improved scores in treatment groups signify the anti-inflammatory potential of *Boswellia serrata*, meloxicam and their combination.

Among haematological indices, RBC count, haemoglobin concentration and PCV of arthritic rats showed a significant drop throughout the experiment while the WBC count and ESR showed a constant rise. Following treatment, all the altered blood parameters showed significant improvement (Tables 2 and 3).

Erythrocyte sedimentation rate (ESR) is an index of the suspension stability of RBCs in plasma and is associated with the number and size of RBCs. In this study, the arthritic rats showed decreased RBC count, reduced haemoglobin (Hb) concentration and elevated ESR levels, which may be due to declined response of bone marrow erythropoietin, destruction of premature RBCs, stress and cell necrosis. These conditions indicate anaemia, which is common in chronic arthritis. Improved RBC count, Hb concentration and ESR to near normal levels in the treatment groups indicates a significant recovery from anaemic condition. These findings were similar to that of Engelhardt *et al.* (1996) in adjuvant induced arthritis animal model.

White blood cell (WBC) count plays a major role in the body's defence mechanism (Patil *et al.* 2012). Increased WBC count is a common feature of inflammatory reactions, especially those induced by microbes. Initially, leucocytosis results from the release of cells from the bone marrow caused by the cytokines Interleukin-1 (IL-1) and Tumour Necrosis Factor- α (TNF- α). It is associated with an increase in the number of relatively immature neutrophils. In this study, the total leukocyte number increased in arthritic control rats, while a significant reduction was noticed in the treatment groups. In cellular defence, Boswellic acids at higher concentrations appear to inhibit lymphocyte proliferation (Ammon 2010). Similar reports by Mishra *et al.* (2011) and Umar *et al.* (2014) suggest that the ability of *Boswellia serrata* to inhibit proinflammatory cytokines might be mediated via modulation of the immune system.

In conclusion, the treatment of experimental adjuvant arthritis with methanolic extracts of *Boswellia serrata* showed a significant restoration which was apparent by a decrease in pain and inflammation marked by reduced paw volume, reduced paw diameter, prolonged paw withdrawal latency, and improved mobility and arthritic scores. This reduction in pain and inflammation may be attributed to the various pharmacologically active principles such as Boswellic acids present in the plant resin. Further, the treatment of arthritic rats with *Boswellia serrata* extract showed a better ameliorative effect when compared to that of the standard anti-inflammatory drug, Meloxicam. Moreover, an enhanced curative effect was also evident when both *Boswellia serrata* and Meloxicam were administered in conjunction.

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