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Ameliorating Effect Of Extracts Of *Alstonia Scholaris* & *Boerhaavia Diffusa* In FCA Induced Arthritis In Wistar Albino Rats

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ABSTRACT

AIM- The aim of the present investigation is to study the anti-arthritic activity of bark of *Alstonia scholaris* & root of *Boerhaavia diffusa* in FCA induced arthritis in Wistar albino rats. **MATERIAL & METHODS-** All the plant materials were dried under shade and subjected to coarse powder for extraction process. Accurately weighed quantity of bark powder of *Alstonia scholaris* were extracted using 95 % ethanol & methanol by soxhlet apparatus for 72 h. Qualitative chemical tests of ethanolic & methanolic extracts were subjected to various chemical tests to detect various phytoconstituents. The acute oral toxicity studies were carried out according to the guidelines set by the Organization for Economic Co-operation and Development (OECD), revised draft guideline 423. The severity of adjuvant arthritis was quantified by measuring the volume of the hind paw using Plethysmograph. Paw volume (ml) was measured at 0 days and thereafter 4, 8, 12, 16 and 21 days of FCA post-inoculation. On the 21st day after arthritis induction, rats were anaesthetized with ether and blood samples were collected into Ethylenediamine tetra-acetic acid (EDTA)-coated tubes from retro orbital junction. **RESULTS-** The preliminary phytochemical analysis revealed that different active constituent present in different extracts such as carbohydrates, proteins, amino acids, fat, oils,

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steroids, terpenoids, glycosides, alkaloids, tannins and other phenolics compounds. The cut off value of 200 and 1/5 dose double of 400 mg/kg were selected for anti-arthritic activity. The assessment made on the 21st day showed that the *A. scholaris* treatments at both doses (low and high) had moderately significant and highly significant effect and reduced ($p< 0.01$& $p<0.001$) the adjuvant-induced lesions in the respective treatment groups as compared with the arthritis control group. This effect was observed from 14th day to last day of the experiment as compared to arthritic rats. All the extracts had moderately and highly significant increase in body weight ($p<0.01$ & $p<0.001$) as compared to arthritic rats. **CONCLUSION-** Besides from the obvious therapeutic importance, these components would be useful in understanding the mechanism of diseases with higher levels of cellular and molecular level.

KEYWORDS-

Ameliorating Effect, *Alstonia scholaris, Boerhaavia diffusa,* FCA Induced Arthritis, Wistar Albino Rats.

INTRODUCTION

Rheumatoid arthritis (RA) is a common chronic and systemic auto immune disease characterized by hyperplasia of the synovial membrane, degradation of cartilage, and erosion of bones in diarthrodial joints. A major unknown in the course of the disease in RA is the reason that inflammation begins and continues within joints often without involvement of other organ systems.

RA is one of many autoimmune diseases that predominate in females. The ratio of female to male patients may vary from 2:1 to 4:1. Pregnancy usually is associated with remission of the disease with subsequent relapses after delivery [1]. The annual incidence of RA is estimated to be about 30 per 100,000 and it affects approximately 0.5%–1.0% of the world population [2].

Clinically, RA is characterized by Polyarthritic, swelling and, in many cases, manifests extra-articular involvement. In the early stage of the disease, typical signs and symptoms are swelling and pain of the proximal interphalangeal and metacarpophalangeal joints. Later, the larger joints become affected, especially those of the arms, feet and knees. In addition, RA

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can affect other systems of the body, and this may range from rheumatoid nodules to life-threatening vasculitis [3].

The aim of the present investigation is to study the anti-arthritic activity of bark of *Alstonia scholaris* & root of *Boerhaavia diffusa* in FCA induced arthritis in Wistar albino rats.

PLANT MATERIALS COLLECTION & AUTHENTIFICATION

The bark of *Alstonia scholaris* were collected from campus of B. R. Nahata College of Pharmacy, Mandsaur. All the plant materials were taxonomically identified by Dr. Gyanendra Tiwari, Senior Scientist, KNK College of Horticulture, Mandsaur. Similarly, roots of *Boerhaavia diffusa* were procured form local market.

PREPARATION OF TOTAL CRUDE EXTRACT

All the plant materials were dried under shade and subjected to coarse powder for extraction process. Accurately weighed quantity of bark powder of *Alstonia scholaris* were extracted using 95 % ethanol & methanol by soxhlet apparatus for 72 h. The ethanolic extracts were dried under the reduced pressure to get crude ethanolic extracts. Roots of *Boerhaavia diffusa* were extracted out by using methanol. After drying, the respective extracts were weighed and percentage yield was determined [4].

PRELIMINARY PHYTOCHEMICAL TESTS

Qualitative chemical tests of ethanolic & methanolic extracts were subjected to various chemical tests to detect various phytoconstituents [5,6].

PRELIMINARY IN-VIVO ANTI-ARTHRITIC ACTIVITY

Selection of animals

Wistar albino rats of either sex between 2 and 3 months of age weighing 150-200 g were used which were procured from the central animal house of College of Pharmacy, India. All animals were housed in an animal room under normal condition of 25±1^{0}C, 12-h light and dark cycle. The animals were allowed free to access commercial rat pallet diet (Lipton India Ltd, Mumbai, India) and water *ad libitum.* The bedding materials of the cages were changed every day. All the experimental procedures were carried out in accordance with the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA) guidelines.

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Acute toxicity studies

The acute oral toxicity studies were carried out according to the guidelines set by the Organization for Economic Co-operation and Development (OECD), revised draft guideline 423.

Evaluation of anti-arthritic activity

The Wistar albino rats were divided into 10 groups of six animals in each. For the induction of chronic inflammatory response, FCA (0.1 ml) was injected through intra-articular injection in left ankle joint of rats on 0 day. Pre-induction baseline was taken prior to the injection of Freund's Complete Adjuvant (FCA) measured by left paw volume of each animal at 0 day for the induction of arthritis in Wistar rats. The treatments with all plant extracts were given once daily from day of injection to 21st day. A suspension of the test extracts were prepared in 1% Tween 80.The animal groups are as follows [7].

Group-I: Arthritic control, treated with 0.1 mL of FCA on zero day.

Group-II: Standard control: treated with prednisolone (10 mg/kg, p.o.) + FCA

Group-V: Treated with ethanolic extracts of *A. scholaris* (200 mg/kg, p.o.) + FCA

Group-VI: Treated with ethanolic extracts of *A. scholaris* (400 mg/kg, p.o.) + FCA

Group-IX: Treated with methanolic extracts of *B. diffusa* (200 mg/kg, p.o.) + FCA

Group-X: Treated with methanolic extracts of *B. diffusa* (400 mg/kg, p.o.) + FCA

Measurements of paw volume

The severity of adjuvant arthritis was quantified by measuring the volume of the hind paw using Plethysmograph. Paw volume (ml) was measured at 0 days and thereafter 4, 8, 12, 16 and 21 days of FCA post-inoculation. Data were expressed as the increase in paw volume with respect to day 0 paw volume. The percentage inhibition of paw volume was measured by following formula [7, 8].

Percentage inhibition=Vc-

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Vt/Vt×100

Where,

Vc-Paw volume of control animals Vt-Paw volume of treated animals

Measurements of body weight

Body weight was measured of all groups at zero days before immunization and at 21st day after treatments over by using a single pan weighing balance [9].

Measurements of hematological parameters

On the 21st day after arthritis induction, rats were anaesthetized with ether and blood samples were collected into Ethylenediamine tetra-acetic acid (EDTA)-coated tubes from retro orbital junction. The number of leukocytes from each rat was determined using a counting chamber (celldyn-1200, Abbott Carepam). Erythrocyte sedimentation rate (ESR) was determined using the Wintrobe method. RBCs and Haemoglobin were determined by routine laboratory method [9].

RESULTS

EXTRACTIVE VALUE DETERMINATION

Dried bark of *Alstonia scholaris* were extracted using ethanol and roots of *Boerhaavia diffusa* were extracted by methanol. The percentage yields of all dried extracts were determined by using the following formula.

$$\text{Percentage yield} = \frac{\text{Weight of Extract}}{\text{Weight of powder drug Taken}} \times 100$$

Table No 1: Different extracts with their appearance and % yield (in gm)

S. No.	Extracts	Color of dried extracts	Consistancy of dried extracts	% Yield (W/W)

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1	Ethanolic extracts of *Alstonia scholaris*	Dark Green	Sticky	21 %
2	Methanolic extracts of *Boerhaavia diffusa*	Dark Brown	Sticky	11 %

PRELIMINARY PHYTOCHEMICAL SCREENING

The preliminary phytochemical analysis revealed that different active constituent present in different extracts such as carbohydrates, proteins, amino acids, fat, oils, steroids, terpenoids, glycosides, alkaloids, tannins and other phenolics compounds.

Table No 2: Qualitative chemical analysis of extracts by chemical tests

S. No	Phytoconstituents	Chemical Tests	*Alstonia scholaris*	*Boerhaavia diffusa*
1	Alkaloids	Wagner's test	+	+
		Dragendorff's test	+	+
		Mayer's test	+	+
		Hager's test	-	+
2	Amino Acid	Millon's test	+	-
		Ninhydrine test	-	-
3	Flavonoids	Shinoda test	+	+
		Alkaline reagent test	+	+
		Zinc hydrochloride test	+	-
4	Phenolics (Tannins)	Gelatin test	+	+
		Phenazone test	-	-
		Ferric chloride test	+	+
5	Protein	Biuret test	+	-
		Hydrolysis test	+	-
		Test with trichloroacetic acid	-	-
6	Triterpenoids & Steroids	Libermann-Burchard test	+	+
		Salkowski test	+	+
7	Carbohydrates	Benedict's test	+	+
		Fehling's test	+	+
		Molish's test	-	-
8	Anthraquinone glycosides	Borntrager's test	+	+
		Modified Borntrager's test	+	+

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9	Coumarin glycosides	_____	-	-
10	Saponin glycosides	_____	+	+
11	Cardiac glycosides	Baljet's test	+	+
		Legal's test	+	+
		Keller-killiani test	+	+

Where, (-) Negative, (+) Positive

ACUTE TOXICITY STUDIES OF PLANT EXTRACTS

No toxic effects were observed at a higher dose of 2000 mg/kg body weight of Wistar rats. Hence, 1/ 10th dose was selected as effective dose or therapeutic dose. The cut off value of 200 and 1/5 dose double of 400 mg/kg were selected for anti-arthritic activity.

ANTI-ARTHRITIC ACTIVITY

Freund's complete adjuvant induced rat paw edema

Observations of paw volume were recorded on 4^{th}, 8^{th}, 12^{th}, 16^{th}, 21^{st} day after adjuvant injection. The CFA-induced arthritic control group showed signs of arthritis development, as seen by the increase in the paw volume and other indications, such as decreased body weight, also showed induction of arthritis in the CFA-treated control group rats. The assessment made on the 21^{st} day showed that the *A. scholaris* treatments at both doses (low and high) had moderately significant and highly significant effect and reduced ($p< 0.01$& $p<0.001$) the adjuvant-induced lesions in the respective treatment groups as compared with the arthritis control group. However, treatments of *Boerhaavia diffusa* had moderately significant effects ($p<0.01$) in treated group as compared to arthritic control.

Table No 3: Effects of extracts on paw volume in FCA induced arthritis in rat

S. No.		Paw Volume in mL					
	Groups & Treatments	Zero Day	4^{th} Day	8^{th} Day	12^{th} Day	16^{th} Day	21^{st} Day
1	Normal Control	0.29±0.08	0.31±0.03	0.31±0.04	0.31±0.01	0.31±0.06	0.31±0.14
2	Arthritic Control, 1% Tween 80, p.o.	0.30±0.02	0.50±0.04***	0.85±0.01***	0.92±0.02***	1.31±0.06***	1.63±0.02***
3	Prednisolone 10 mg/kg, p.o.	0.31±0.07	0.33±0.06*	0.40±0.18***	0.45±0.03***	0.52±0.04***	0.55±0.08***

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4	*A. scholaris*, 200 mg/kg, p.o.	0.31±0.06	0.44±0.07	0.52±0.02*	0.63±0.05 *	0.70±0.09 **	0.77±0.14 **
5	*A. scholaris*, 400 mg/kg, p.o.	0.33±0.04	0.42±0.12	0.50±0.01*	0.58±0.03 **	0.62±0.02 **	0.68±0.03 ***
6	*B. diffusa*, 200 mg/kg, p.o.	0.30±0.04	0.48±0.13	0.70±0.002	0.75±0.10 *	0.82±0.06 **	0.88±0.01 **
7	*B. diffusa*, 400 mg/kg, p.o.	0.31±0.08	0.47±0.04	0.68±0.11*	0.70±0.03 **	0.76±0.02 **	0.80±0.11 ***

Values are expressed as mean±SEM, n=6 in each group; * p <0.05, compared to disease control ** p<0.01, compared to disease control. *** p <0.001, compared to disease control

Effects on body weight

Although the weights were almost identical in all group of animals at 0 to 7 days during the subsequent course of disease, the body weight always declined in arthritic control group from 14th day to 21st day. In arthritic group, decrease in body weight were observed on the subsequent days, whereas groups treated with standard, extracts of *A. scholaris* and *B. diffusa* showed improvements in body weight. This effect was observed from 14th day to last day of the experiment as compared to arthritic rats. All the extracts had moderately and highly significant increase in body weight (p<0.01 & p<0.001) as compared to arthritic rats.

Table No 4: Effects of plant extracts on body weight in FCA induced arthritis in rat

S. No.	Groups & Treatments	Days	
		Zero	21st
1	Normal Control	190.20±0.78	191.47±0.20
2	Arthritic Control, 1% Tween 80, p.o.	191.40±0.18	165.18±0.20***
3	Prednisolone, 10 mg/kg, p.o.	191.80±0.20	216.30±0.16***
4	*A. scholaris*, 200 mg/kg, p.o.	190.18±0.12	208.40±0.12**
5	*A. scholaris*, 400 mg/kg, p.o.	192.25±0.40	211.60±0.02***
6	*B. diffusa*, 200 mg/kg, p.o.	190.65±0.38	202.30±0.19*
7	*B. diffusa*, 400 mg/kg, p.o.	192.30±0.18	204.80±1.12**

Values are expressed as mean±SEM, n=6 in each group; *p<0.05, compared to disease control ** p<0.01, compared to disease control. ***p<0.001, compared to disease control

Effects on haematological parameters

FCA-induced arthritic rats at 21st day showed elevation in the total WBC count and reduction in RBC. However, significantly *(p<0.001)* increased ESR while the

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haemoglobin was significantly *($p<0.001$)* reduced in the control group when compared with normal group. However, standard, and *A. scholaris* had highly significant effects ($p<0.001$) in recovery of RBCs and haemoglobin. They also showed highly significant effects on decrease in WBCs and ESR. *B. diffusa* extract treated groups, also showed moderately significant effects as compared to arthritic group.

Table No 5: Effects of extracts on haematological parameters in arthritis in rat

S. No.	Groups & Treatments	Haematological Parameters			
		Total WBCs count×10^3 cells/mm^3	**RBCs (Million/$mm)^2$**	**Haemoglobin (g/dl)**	**ESR (mm/h)**
1	Normal Control, 1% Tween 80, p.o.	8.18±0.90	7.88±0.11	14.82±0.13	11.40±0.42
2	Arthritic Control, 1% Tween 80, p.o.	14.70±1.12***	5.36±0.16**	10.46±0.12**	15.80±0.18***
3	Prednisolone 10 mg/kg, p.o.	8.48±0.75***	7.90±0.08**	15.20±0.31***	11.90±0.12***
4	*A. scholaris*, 200 mg/kg, p.o.	11.58±0.26*	6.10±0.09**	12.10±0.31*	13.72±0.10**
5	*A. scholaris*, 400 mg/kg, p.o.	10.86±0.21**	6.58±0.19*	12.64±0.82**	13.18±0.32**
6	*B. diffusa*, 200 mg/kg, p.o.	13.10±0.12*	5.72±0.16*	11.30±0.28*	14.20±0.26*
7	*B. diffusa*, 400 mg/kg, p.o.	12.52±0.51*	5.84±0.07*	12.15±0.18*	13.78±0.14**

Values are expressed as mean±SEM, $n=6$ in each group; *$p<0.05$, compared to disease control ** $p<0.01$, compared to disease control. ***$p<0.001$, compared to disease control

DISCUSSION

The disease progresses rapidly over several weeks in what appears clinically to be a monophasic process. Granulocytes and auto reactive CD4 cells play major roles in the disease. Humoral immune mechanisms appear not to contribute to the disease process. This unique rat disease model represents a systemic process that involves not only the joints but also the gastrointestinal and genitourinary tracts, the skin and the eyes [10]. The appearance of primary lesions, i.e. injected paw swelling is a manifestation of release of various cytokines and cell-mediated immunity response [11]. All the test extracts were found to effectively reduce the

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primary lesions in arthritic rats. The suppression of this response therefore suggests any immunosuppressive activity for our test extracts. Moreover, this effect of test extracts was comparable to that of prednisolone. Our study results reveal that extracts of *Alstonia scholaris & Boerhaavia diffusa* treated rats significantly reduced the paw volume. During the development of arthritic syndrome, the body weight of rats used as an indirect index in restoration of health. The body weight was significantly decreased in arthritic rat as compared to normal rat, but in the test extracts and standard drug treated groups, the body weights of the rats did not decline. The results of our study therefore indicated that there is a relationship between the extent of inflammation and loss of body weight. As the incidence and severity of arthritis increase, the changes in the body weights of the rats also occur during the course of the experimental period [12]. Previous findings suggest that absorption of ^{14}C- glucose and ^{14}C-leucine in rat's intestine was reduced in the case of inflamed rats [13] but on the treatment with anti-inflammatory drugs, the decrease in absorption is neutralized. In our study, the body weight was significantly increased in the groups treated with prednisolone and all the extracts treated groups and this may be due to the restoration of absorption capacity of intestine. With the development of arthritic conditions, there was a significant alteration of haematological parameters i.e. red blood cells (RBCs), white blood cells (WBCs), Haemoglobin (Hb) and erythrocyte sedimentation rate (ESR). As the disease progressed, RBCs and haemoglobin were decreased whereas; WBCs and ESR were significantly increased in arthritic control group when treated with normal control. It was proposed that the reduction in the Hb and RBC count during arthritis results from premature destruction of red blood cells, reduced erythropoietin levels and also due to abnormal storage of iron in the reticuloendothelial system and synovial tissue [14]. In addition an increase in ESR is a common feature in rheumatoid arthritis and this increase in the ESR is attributed to the accelerated formation of endogenous proteins such as fibrinogen and a/b globulin, and such a rise in the ESR indicates an active but obscure disease process. The results of our study revealed that all the extracts treated group's causes significant alterations in the hematological parameters and maximal effects were observed at 400 mg/kg. The reversal of RBC counts and Hb levels observed in case of test extract treated groups could be attributed to the protective effects on tissue repair and suppression of disease progression. By modulation of

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immune system, all the extracts and prednisolone treated groups normalize the WBCs and ESR. In previous literature, a lots of biologically active phytocompounds such as steroids, flavonoids, alkaloids, terpenoids, glycosides, tannins and phenolic compounds are reported to be responsible for significant anti-arthritic and anti-inflammatory activity [15].

In our phytochemical screening, all the extracts had shown the presence of active phytocompounds i.e. steroids, terpenoids, alkaloids, flavonoids, glycosides and fatty acids. Preliminary anti-arthritic activity of selected plants extracts was clearly demonstrated that all the selected plants have significant anti-arthritic activity and presence of aforementioned phytocompounds in the extracts may be responsible for the anti-arthritic activity. By comparing the results of the selected plants in FCA induced arthritis, it could be concluded that ethanolic extracts of *Alstonia scholaris* & methanolic extract of *Boerhaavia diffusa* have most potent and highly significant anti-arthritic activity.

CONCLUSION

Besides from the obvious therapeutic importance, these components would be useful in understanding the mechanism of diseases with higher levels of cellular and molecular level. These components could serve as lead molecules for development of prospective anti-arthritic agents. Further detailed studies are required to elucidate the exact mechanism based on molecular and genetic level responsible for anti-arthritic activity.

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