RESEARCH ARTICLE

Atalantia Racemosa Wight Mitigates Arthritis Through the Modulation of Crucial Immune Mediators of Inflammation in an Experimental Arthritis Model

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ABSTRACT

Objective

The persistent need to discover plant species with anti-arthritic properties prompted the investigation of *A. racemosa* Wight. The objective is to study anti-arthritic attributes of ethanolic extracts made from *A. racemosa* leaves and stems.

Methods

Using in vivo model, the anti-arthritic property was evaluated. Acute toxicity was performed as per OECD strategies to determine dose. Formaldehydeinduced model was used to investigate anti-arthritic action. 200 mg/kg of ethanolic extracts of leaves and stems were given orally. To know the antiarthritic potential of *A. racemosa* radiology as well as histopathology was performed.

Results

The stem ethanolic extract demonstrated significant reduction in arthritis by showing 49.65% inhibition than leaf ethanolic extract which shows 38.89% inhibition. Chemical examination of the plant's ethanolic leaf and stem extracts shown existence of flavonoids, terpenoids, and steroids. Antiarthritic activity of *A. racemosa* is supported by histopathology, radiology and haematological analysis.

Conclusion

This study indicates that A. racemosa may be useful as a bioactive chemical source for the treatment of inflammatory disorders and orthopedic pain.

Key Word: Stems, Leaves, Anti-arthritic activity, Histopathology, Radiology.

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INTRODUCTION

Arthritis, a chronic inflammatory complaint distressing joints, is a leading cause of disability worldwide. Conventional treatments often exhibit limited efficacy and are associated with adverse effects.[1-3] Hence, there is a growing interest in exploring natural sources for potential anti-arthritic agent.*A. racemosa* Wight, a medicinal plant found in various regions, has been traditionally used for management of asthma, bronchitis, allergy, cough, etc.[4-6] Plant extracts are analysed for phytochemical screening in order to find bioactive chemicals. The therapeutic qualities of medicinal plants are frequently influenced by these secondary metabolites. *A. racemosa* may include alkaloids, flavonoids, terpenoids, steroids, and other constituents, according to preliminary phytochemical analyses.[7,8] Furthermore, a comprehensive pharmacological assessment is necessary to ascertain *A. racemosa's* anti-arthritic effect. To investigate the mechanisms behind its anti-arthritic properties, in vivo investigations will be carried out, with a specific focus on pathways implicated in the etiology of arthritis. Comprehending the pharmacological characteristics of this plant can yield significant knowledge for creating novel treatment approaches to combat arthritis.[9-11]

A. racemosa Wight often called wild lime, is an evergreen up to medium sized tree in the Rutaceae family[12]. It can tolerate a variety of soil types and grows well in tropical and subtropical environments[13,14]. The lanceolate, glossy leaves, fragrant white flowers in racemes, and spherical to ovoid berries that mature to orange or yellow are the morphological characteristics of *A. racemosa*. Many plant parts, including leaves, fruits, and bark, are used in Ayurvedic medication due to their supposed anti-inflammatory and digestive qualities. The plant's usage in traditional medicine dates back many years[15,16]. The plant's historic applications and the necessity for more research motivate the decision to start a thorough investigation that includes phytochemical screening and pharmacological evaluations[17].

This research aims to bridge the traditional knowledge of *A. racemosa* with modern scientific methods, laying the groundwork for its utilization as a potential anti-arthritic agent. To further understand the therapeutic potential of *A. racemosa* in the context of arthritis care, it is important to

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Table 1: Anti-arthritic activity

Groups	PawEdema in Mm					
	Day0	Day2	Day4	Day6	Day8	Day10
Group I	3.93±0.05 ^{ns}	3.95±0.23 ^{ns}	3.96±0.56 ^{ns}	3.99±0.42 ^{ns}	3.98±0.15 ^{ns}	3.77±0.19 ^{ns}
Group II	4.65±0.08 ^{ns}	8.92±0.17*	11.621±0.34*	11.54±0.19*	11.57±0.34*	11.62±0.39*
Group III	3.79±0.18 ^{ns}	7.31±0.26**	9.72±0.34**	7.5±0.35**	4.91±0.42**	4.83±0.26**
Group IV	4.69±0.24 ^{ns}	8.84±0.54**	10.33±0.23**	9.42±0.24**	6.19±0.47**	5.85±0.15**
Group V	3.59±0.22 ^{ns}	8.27±0.18***	10.18±0.28***	9.33±0.48***	7.23±0.47***	7.1±0.32***

The results showed a one-way ANOVA followed by a Dunnet t test, and they are presented as the mean ± SEM (n=6). With a p-value of 0.05 or higher, it is not clinically significant. A significance level of *P <0.05, **P <0.01, and ***P <0.001 was set. as compared to the arthritis control group.

combine phytochemical screening with pharmacological investigation.

MATERIALS AND METHODS

Materials

Plant material: Originating in Satara, Maharashtra, the *A. racemosa* plant was gathered from Kas platue.The botanical specimen was placed in Botanical Survey of India's repository in Pune, accompanied by a voucher specimen number Ref. No.BSI/WRC/Iden. Cer./2021/2505210007300. The stem and leaves were dried under shade and converted to powder.

Extract Preparation

The Soxhlet device was used to extract both powder materials using ethanol as the solvent[18]. After drying the extract, the yield was quantified[19,20].

Preliminary testing for phytochemicals

To find the phytocomponents in the extracts, phytochemical screening was performed[21,22].

Experimental animals

Experimentations were carried out using Wistar Albino rats from animal house and for seven days leading up to

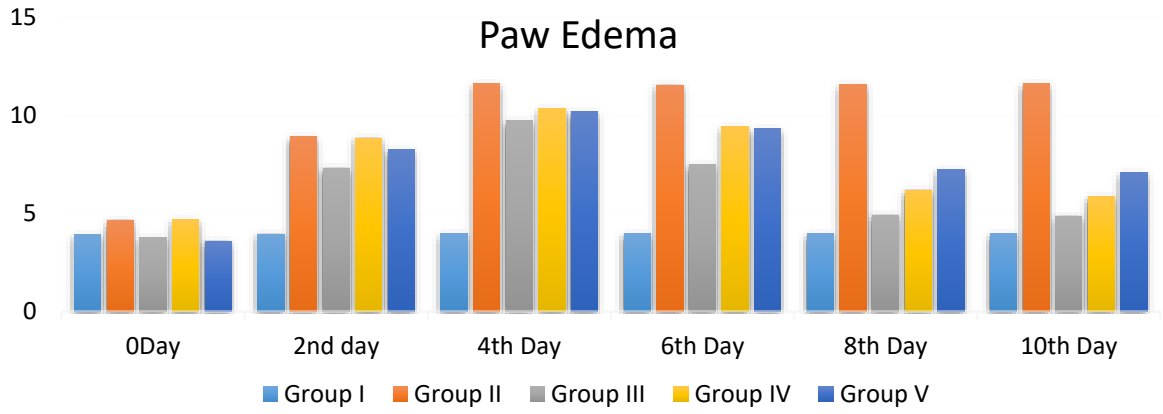

Figure 1: Change in paw edema in arthritis induced by Formaldehyde

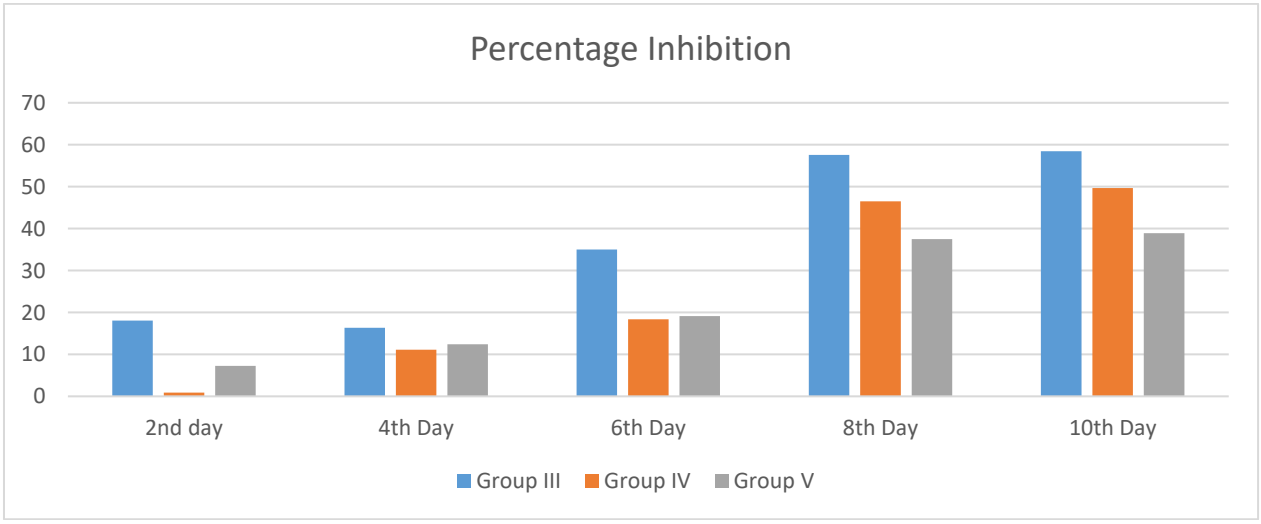

Figure 2: Percentage inhibition of Formaldehyde induced paw edema

Table 2: % inhibition of paw edema

Groups	Day2	Day4	Day6	Day8	Day10
Group III	18.05	16.35	35.00	57.56	58.43
Group IV	0.89	11.11	18.37	46.49	49.65
Group V	7.28	12.4	19.15	37.51	38.89

the experiment, the room was kept at standard temperature and humidity, with the animals fed a standard rodent food and given unlimited access to water. The experimental conditions were maintained by keeping temperature at 22± 2°C and the relative humidity at 55± 5%. When required, animals were fed nothing for twelve hours before an experiment. This investigation was permitted by Animal Ethical Committee of Invitox R and D institute, Undri, Pune (IRDI/IAEC/M03/05/2024-25)[23].

Acute toxicity study

Wistar albino rats were used in this study in accordance by OECD guidelines, with three rats per group and the ethanolic extracts of leaves and stems were administered by oral gavage. These animals were observed for 24hrs and daily for 7 days[24].

Anti-arthritic activity

Arthritis induced by Formaldehyde

This model is used for assessing chronic anti-inflammatory effect of different drugs. This model is closely related with human arthritis[25]. 5 groups of 6 rats were made such as Group I: received 3ml/kg distilled water p. o., Group II: received Formaldehyde 0.1 ml (2%), Group III: received indomethacin 3mg/kg p.o., Group IV and V: Treatment groups which receives ethanolic extract of stem and leaves respectively (200mg/kg p.o.). On the 1st and 3rd day of the experiment, rats were injected with a formaldehyde solution into subplantar area of right hind paw in order to induce a chronic phase of inflammation. For a duration of 10 days, the oral administration of Indomethacin and both extracts was carried out[26]. Paw thicknesses of rats were measured on days 0, 2, 4, 6, 8 and 10 using a digital caliper.[27] The % inhibition of paw edema was determined[28].

Using CO_2 as an anesthetic, animals were sacrificed at the last stage of the experiment[29]. RBCs, WBCs, and haemoglobin contents were measured in blood samples that were obtained via the retro-orbital method.[30] Rats with arthritis produced by formaldehyde had their proximal interphalangeal joints removed, preserved in 10% formalin, and used in histological investigations. The radiographs were taken of the hind legs[31].

Assessment of haematological parameters

Assessment of RBC, WBC counts, haemoglobin content and erythrocyte sedimentation rate were carried out. Also, C-reactive protein (CRP) was measured using standard kits.

Radiological study

The experimental animal's hind paws were radiographed

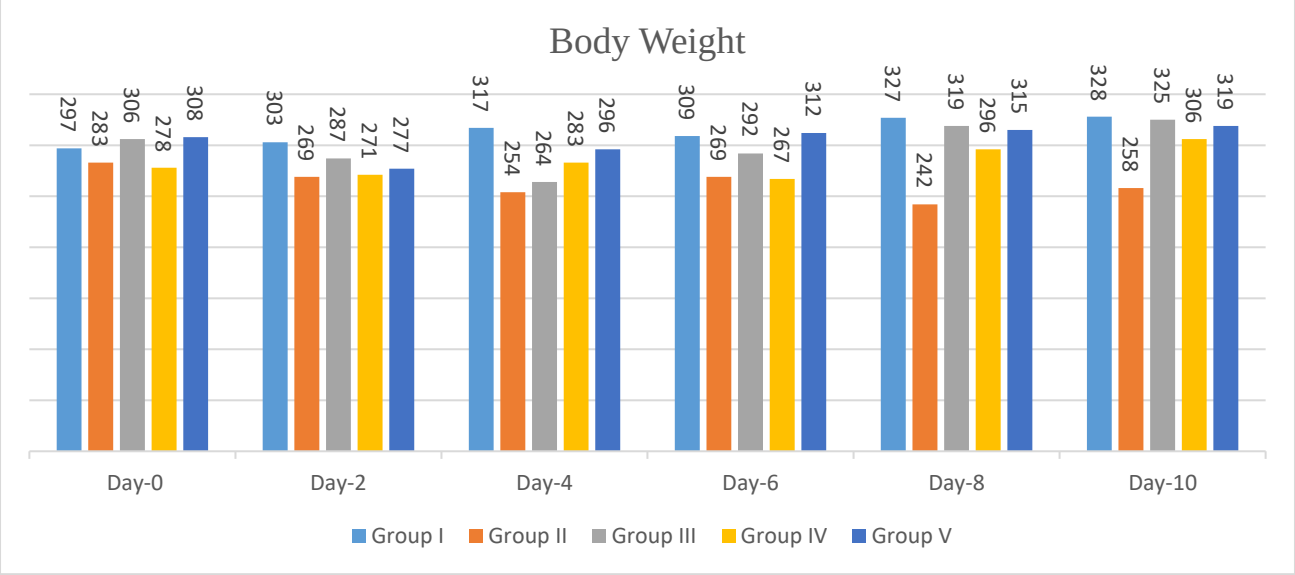

Figure 3: Body weight determination

Table 3: Body weight determination

Groups	Body weighting					
	Day0	Day2	Day4	Day6	Day8	Day10
Group I	297±17^{ns}	303±14^{ns}	317±26^{ns}	309±18^{ns}	327±29^{ns}	328±31^{ns}
Group II	283±26^{ns}	269±39*	254±43*	269±37*	242±13*	258±28*
Group III	306±27^{ns}	287±32**	264±23**	292±22**	319±37**	325±43**
Group IV	278±31^{ns}	271±47***	283±36***	267±27***	296±32***	306±38***
Group V	308±24^{ns}	277±19***	296±13***	312±21***	315±23***	319±39***

The data are presented as the mean ± SEM (n=6), produced by a one-way ANOVA followed by a Dunnet t test. P≥0.05 indicates that the result is not significant. The significance levels are as follows: *P <0.05, **P <0.01, and ***P <0.001. in contrast to the arthritis control group.

Table 4: Effect on haematological parameters

Groups	Treatment and Dose	Hb mg/dl	WBC $X10^3$/ mm^3	RBC $X10^6$/ mm^3	ESR (10^6 Cells/ µl of blood)
I	Normal	12.8±1.12	6.1±0.23	6.54±0.46	4.99±0.23
II	Control	09.8±0.78*	15.4±0.65*	4.36±1.02*	15.89±0.58*
III	Standard	11.9±0.36**	10.3±0.34**	5.54±0.46**	6.75±0.84**
IV	Ethanolic Extract of stem	11.1±1.12***	10.1±0.78***	6.07±0.65***	6.14±0.69***
V	Ethanolic Extract of leaves	10.7±0.89***	12.4±0.56***	5.04±0.46***	7.10±0.39***

Findings are presented as the mean ± SEM (n=6), after a one-way ANOVA and a Dunnet t-test. There is no statistical significance, with a p-value of 0.05 or higher. ***P <0.001, **P <0.01, *P <0.05 contrasted with the arthritis control group.

Table 5: Effect on C reactive proteins

Groups	Treatment and Dose	CRP (mg /L)
I	Normal	6.34±0.68
II	Control	12.47±0.48*
III	Standard	7.63±0.65**
IV	Extract of stem of *A. racemosa* plant	8.56±0.48***
V	Extract of leaves of *A. racemosa* plant	10.47±0.78***

Findings are presented as the mean ± SEM (n=6), after a one-way ANOVA and a Dunnet t-test. There is no statistical significance, with a p-value of 0.05 or higher. *Compared to the arthritis control group, *P <0.05, **P <0.01, ***P <0.001.

and checked for bone erosion[32].

Histopathological study

The hind paw was taken apart, the interphalangeal joints were cleaned with saline, and 10% formalin was applied for 24 hours. Eosin-hematoxylinstain was applied to the sections and they were studied below an optical microscope[33].

Statistical analysis

The mean ± SEM is utilised in the data. Two statistical tests, Dunnet's multiple comparison test and one-way ANOVA were used.

RESULTS

Preliminary testing for phytochemicals

The ethanolic stem extract had a yield of 7.6% and the leaf extract of 9.5%. The initial phytochemical examination uncovered a variety of compounds, including glycosides, alkaloids, saponins, terpenoids, and flavonoids.

Acute oral toxicity study

The ethanolic stem and leaf extract was safe and effective up to 2000 mg/kg. For this reason, the in vivo actions were evaluated at a dosage of 200 mg/kg.

Anti-arthritic activity

The result was given in Table 1. On 10^{th} day, treatment with both extracts significantly reduced swelling in comparison to the arthritis induced group. % inhibition of paw edema on the 10^{th} day was 58.43% for the standard, 49.65% for the ethanolic extract of stems, and 38.89% for the ethanolic extract of leaves (Figure 1, Figure 2, Table 2).

Analysis of body weight

Table 3 shows the weight gain for each treatment group on the tenth day relative to their starting weight. The rats in the arthritis control group experienced a loss in body weight, whereas those treated with extracts and indomethacin exhibited rise in body weight (Figure 3).

Haematological analysis

In arthritic control group, WBC count rises while RBC count and haemoglobin content reduces significantly. In contrast, the groups treated with the ethanolic extracts of stem and leaves, and standard treatment, exhibited a momentous rise in RBC count and haemoglobin content, and their WBC count was almost normal (Table 4). C Reactive proteins found to be increased during inflammation. In arthritic group CRP levels are high while in the standard as well as extract treated group these levels are less (Table 5).

Histopathology

Rat joint with arthritis-induced alterations from normal hind paw joint are demonstrated by histopathology. Arthritic hind paw joints exhibit abnormalities, such as an uptick in synovial hyperplasia and inflammatory cell infiltration, when examined. Structural changes were observed showing severe abnormality. While the histopathology of extract treated groups shows no pathological changes, no inflammatory infiltration hence no abnormality was observed and thus exhibit a normal structure. And the standard treated group shows mild hemorrhage but no pathological changes as well as inflammatory infiltration and thus exhibited a normal structure. (Figure 4)

Radiological analysis

Rat joints radiographs in arthritis-induced rat model illustrate subsequent finding. (Figure 5). It showed bone degeneration, joint space constriction, and soft tissue edema. While the extract-treated groups displayed reduced bone deterioration, joint space narrowing and oedema of soft tissues. On other hand, the group that received standard did not have any bone deterioration.

DISCUSSION

In order to determine the phytoconstituents, we first performed a preliminary phytochemical study and measured the percentage yields of the extracts. Following OECD criteria, an acute toxicity investigation was carried out. No adverse effects or fatalities were recorded at dosages up to 2000 mg/kg p.o., suggesting safety. Using a digital caliper, we examined the changes in paw edema of rats that had been induced to arthritis by

formaldehyde.According to the results, ethanolic stem extract was effective in reducing edema, whereas the ethanolic leaves extract had a moderate effect.

The reduction in hemoglobin level and RBC count in the arthritic control group demonstrates anemia in the arthritic rats. Between 30 and 60 percent of RA patients will experience anemia, making it one of the most prevalent extra-articular symptoms of the disease[34]. Arthritis patients

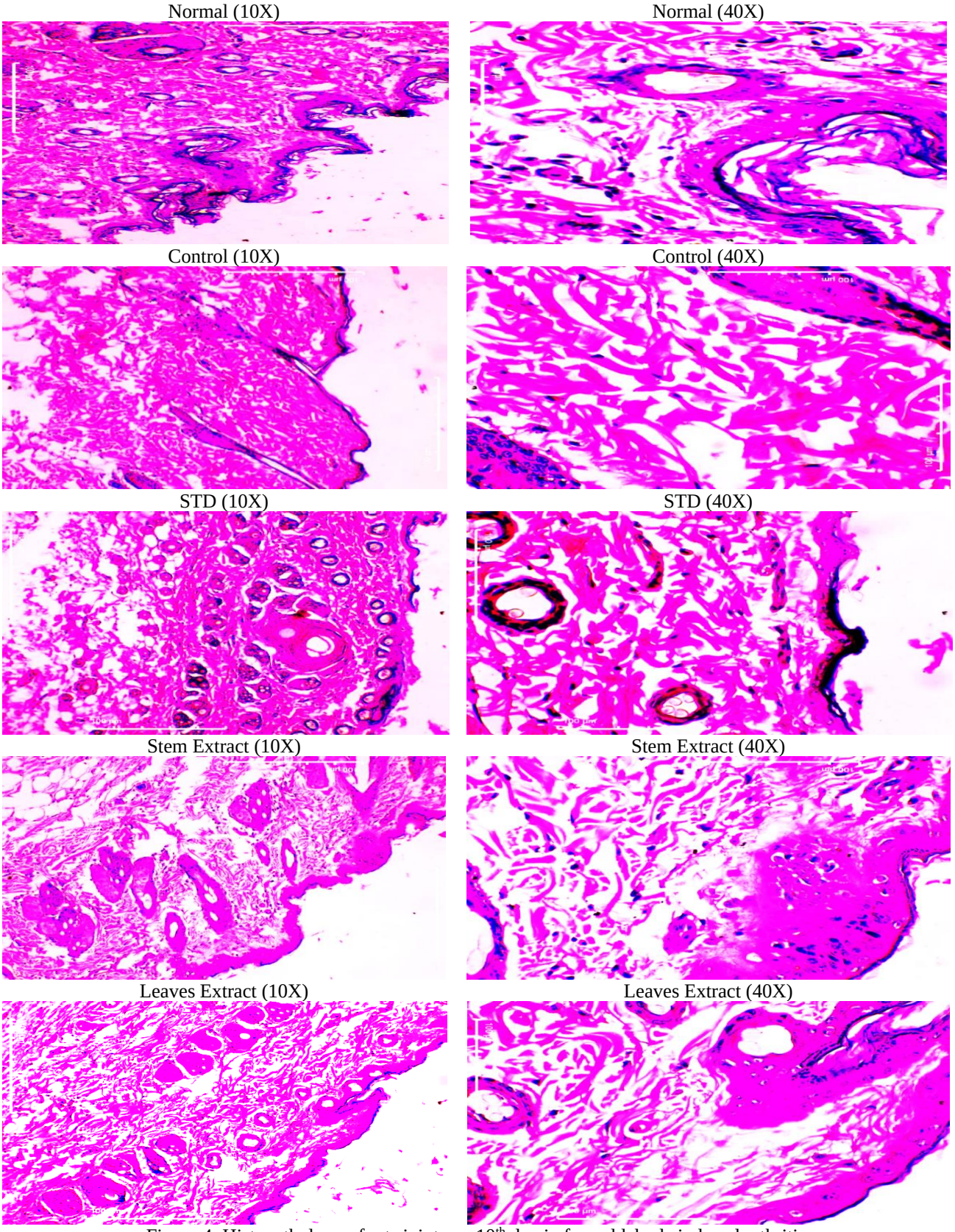

Figure 4: Histopathology of rats joints on 10th day in formaldehyde induced arthritis

often experience anemia due to two main causes: changes in bone marrow function and gastrointestinal blood loss induced by long-term use of NSAIDs, which inhibit the release of iron for RBC integration. Both the standard treatment and the groups given the ethanolic extracts of the leaves and stems had a marked improvement in the symptoms of anemia. Increased WBC count in the arthritis control group was most likely the result of immune system activation in response to invader antigens. Treatment groups' markedly reduced white blood cell counts attest to their immunomodulatory effects[35].

C-reactive protein (CRP) is an acute phase protein that has long been used as a marker for systemic inflammation. Inflammation causes an increase in both IL-6 and C-reactive protein (CRP) levels in the plasma, which are produced by adipocytes[36] and macrophages[37] respectively. The arthritic rat group had significantly higher C-reactive protein levels than the control and extract groups, according to the results. Restoring CRP levels to near-normal in both the standard and extract treatment groups was achieved by inhibiting the release of inflammatory mediators.

There are clear distinctions between the ankle joints of healthy rats and those with arthritis, according to histopathological investigations. Common abnormalities seen in arthritic joints include swelling, cartilage degradation and partial destruction, bone marrow deterioration, and a substantial inflammatory exudate infiltration on the articular surface. The histopathology of the hind paw joints of rats that were given arthritis showed that the joints had significant abnormalities, such as the removal of bone marrow and a lot of cells on the surface of the joint. Nevertheless, these pathological conditions were significantly reduced after treatment with the ethanolic extract of the stems and leaves, suggesting that they have antiarthritic activity and protect against bone deterioration.

One useful diagnostic tool for gauging the severity of RA is the disease's impact on radiographic abnormalities. Before more severe changes, such as bone disintegration

Figure 5: Radiographs taken on the tenth day after formaldehyde-induced arthritis in rats.

and joint space constriction, become apparent on radiographs, rheumatoid arthritis manifests primarily as soft tissue swelling[38]. The present research shown that extracts from stems and leaves can help reduce swelling in soft tissues and reduce joint spaces, especially in the early phases of arthritis. There is strong evidence from radiographic studies that the extracts have anti-arthritic effects.

CONCLUSION

A. racemosa stem ethanolic extract had a stronger antiarthritic effect than *A. racemosa* leaf extract, according to an evaluation of the two extracts. The ethanolic stem extract may have more active compounds because it contains flavonoids. Further investigation into the molecular mechanism behind the antiarthritic action of ethanolic stem extract may be necessary to solidify its position as a prospective alternative treatment for arthritis.

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