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Phytochemical Investigation and Anti-Arthritis Potential of Ficus Elastica in Experimental Animals

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The current work uses a Wistar albino rat model of arthritic arthritis caused by Freund's adjuvant to assess the antiarthritic properties of an ethanol extract of Ficus elastica leaves (EEFE). For a preliminary phytochemical analysis, EEFE were tested. The OECD-425 criteria were followed when conducting acute oral toxicity studies. In Freund's adjuvant-induced rat model, the antiarthritic effects of EEFE at 200 mg/kg/p.o. and 400 mg/kg/p.o. were assessed. It was discovered that EEFE's LD50 was more than 2000 mg/kg/p.o. When compared to the arthritic control rats, the highest reduction in rat paw oedema volume in Freund's adjuvant-induced rat model was 71.56 for EEFE (400 mg/kg) and 39.11% for Diclofenac therapy. The arthritic control rats' abnormal haematological and biochemical parameters returned to normal after receiving EEFE treatment at dose levels of 200 mg/kg/p.o. and 400 mg/kg/p.o. The antiarthritic efficacy of

EEFE was validated by radiological assessment. Clinical, biochemical, and radiological tests revealed that EEFE exhibited strong antiarthritic action. Although the current study shows that EEFC has antiarthritic properties, more research is needed to determine how it works.

1. Introduction

Polyarticular symmetrical arthritis is a hallmark of rheumatoid arthritis, a systemic autoimmune disease. If treatment is not received, a number of inflammatory mediators can cause joint inflammation, discomfort, loss of function, joint deterioration, and irreversible deformity. [1] Rheumatoid arthritis affects between 0.5–1.0% of people worldwide, and its prevalence is constant. People between the ages of 25 and 55 are typically affected. At a ratio of three to one, women are impacted more frequently than men. Angiogenesis, mononuclear infiltration, and synovial hyperplasia are its defining features. It develops in three phases. [2] The synovial lining swells in the first stage, resulting in joint pain, warmth, stiffness, redness, and swelling. The second factor is the cells' quick development and division, which thickens the synovium. The affected joint frequently loses its shape and alignment in the third stage due to the production of enzymes by the inflamed cells that may break down bone and cartilage, resulting in excruciating pain and limited mobility.[3, 4]

Glucocorticoids, such as cortisone and prednisone, NSAIDS, such as Ibuprofen and naproxen, disease-modifying anti-inflammatory and anti-rheumatic medications, such as methotrexate (MTX) and leflunomide, and more recent treatments, such as biological response modifiers, such as tumour necrosis factor, alpha blocking agents, anti-CD 20 therapy (rituximab), and abatacept, are frequently used to reduce or stop the underlying immune processes. [5, 6, 7, 8] In addition to their expensive price, all of these medications have a number of negative side effects, serious adverse reactions, and toxicity. Some patients receiving biological response modifiers may also be at risk for infection. In order to find medications that are long-acting anti-inflammatory treatments with few adverse effects, researchers are now turning to the traditional medical system.[9, 10, 11]

The World Health Organisation recognises the value of natural goods as an alternative to pharmaceutical ingredients that the vast majority of people on the planet can afford. [12, 13, 14] Furthermore, a number of studies have shown the positive benefits of natural chemicals and the potential for antioxidants in certain medicinal plants. [15, 16] The rubber tree, or Ficus elastica, is a significant medicinal plant that is a member of the Moraceae family. [17] The pharmacological qualities of F. elastica plants, which are widely cultivated throughout Asia [18], include anti-inflammatory [20], anti-cancer [21], and antioxidant [19]. Flavonoids, essential oils, anthocyanins, tannins, and other phenolic components are said to be abundant in Ficus species. [22] Compounds such rutin, luteolin, coumarins, quercitrin, kaempferin, myricitrin, syringin (eleutheroside B), and morin are found in F. elastica. [23] Antioxidant activity found in the leaves of F. elastica can be used to treat skin allergies and infections. [18] Hence, the present study has aim to determined the medicinal properties of F. elastica for their potential as anti-arthritis.

2. MATERIALS AND METHODS

Materials: Ethanol, Methanol, Chloroform (Rankem, New Delhi), Carboxy methyl cellulose (Loba Chemie, Mumbai), and Diclofenac sodium (Akums Drugs and Pharmaceuticals, India). The chemicals used were Freund's Complete Adjuvant Injection (Sigma Chemicals, USA). All the drugs used in this study were of pharmaceutical grade.

Preparation of F. elastica Extract: The nearby Bhopal area provided the leaves of F. elastica L. Approximately 85 grammes of dehydrated F. elastica leaves were crushed, and 400 millilitres of 70% ethanol solvent were employed for extraction. The ethanol filtrate was collected every 24 hours until it turned colourless. [24] In order to obtain extract, this maceration process used an evaporator set to 50°C. F. elastica extract weighing up to 2.12 g was kept at -20°C.

Preliminary phytochemical screening: Phytochemical analysis was performed using standard procedures to identify the phytoconstituents present in the leaves of Ficus elastica as described by Kokate. [25]

Experimental animals: Male Albino rats weighing between 150 and 200 grammes were used in all of the tests. This study's Institutional Ethical Committee examined all experimental protocols and procedures. Every animal was kept under typical laboratory settings in cages made of polypropylene. The temperature and relative humidity of the animals' housing were 24±2°C and 60–70%, respectively. They were given a regular feed and unlimited water, and they were allowed to acclimatise to the circumstances of the animal house for a week. Water was available without charge, however all trials were carried out following an overnight fast. [26]

Acute oral toxicity study: In accordance with OECD guidelines 425, an acute oral toxicity study (EEFE) was carried out. A single rat was given the test doses of EEFE, 300 mg/kg and 2000 mg/kg, orally. Four animals were dosed with EEFE and two more animals were dosed with EEFE if mortality was not seen. Up to 48 hours, they were monitored for mortality and significant morphological changes. [27]

Freund's adjuvant induced arthritis: Each group employed a minimum of six animals. Four groups of male albino rats were created: control, standard, and drug-treated (two groups receiving low and high doses of ethanolic extract). Group 1 was the control group, receiving 1% CMC (1 ml/1 kg body weight); Group 2 was the standard group, receiving 15 mg/kg of diclofenac sodium suspended in CMC; Group 3 was the first test group, receiving 200 mg/kg of ethanolic extract orally; and Group 4 was the final group, receiving 400 mg/kg of ethanolic extract orally. [28]

0.1 cc of Freund's complete adjuvant (FCA) was injected into the left hind paw's planter region in rats. On the day of the adjuvant injection, body weight was noted and the paw volumes of both hind paws were measured with a plethysmometer. For 14 days following the day of Freund's adjuvant injection, oral dosages of diclofenac sodium (15 mg/kg) and an ethanolic extract of the plant's leaves (200 and 400 mg/kg) were given. Up to 21 days after Freund's adjuvant injection, measurements were taken of the paw volume variations on different days. On the first, seventh, fourteen, and twenty-first days following the adjuvant injection, the mercury plethysmometer was used to measure the change in the inflammatory reaction. On

the first, seventh, fourteen, and twenty-first days following the adjuvant injection, the animals were weighed using a digital weighing balance. All animals were put to sleep on the twenty-first day of the trial, and blood was extracted via retroorbital puncture and collected in plain and EDTA-containing tubes for serum separation, respectively. Biochemical tests such as serum glutamate pyruvate transaminase (SGPT), serum glutamate oxaloacetate transaminase (SGOT), alkaline phosphatase (ALP), and bilirubin were performed on the homogenised samples. [29]

Radiological studies: All experimental animals had their hind paws radiographed, and the images were analysed for soft tissue swelling, bone erosions, and narrowing of the joint spaces. [30]

Statistical analysis: Using the statistical software program Graph Pad Prism, version 5.03, ANOVA and the Bonferroni test were used for statistical analyses. $P<0.05$ was regarded as statistically significant, and values were presented as mean ± SEM. [31, 32]

3. RESULTS AND DISCUSSION

RESULTS

Preliminary phytochemical screening: The yield percentage that was attained was 2.49%. EEFE contained tannins, saponins, glycosides, flavonoids, steroids, and terpenoids, according to a preliminary phytochemical examination..

Acute oral toxicity study: Up to 300 and 2000 mg/kg oral doses, EEFE did not exhibit any harmful or toxic effects, demonstrating non-toxicity even at larger dosages. It was discovered that the LD50 of EEFC was over 2000 mg/kg. In order to assess in vivo antiarthritic effectiveness in Freund's adjuvant-induced arthritic rat model, 200 mg/kg and 400 mg/kg were chosen as the doses.

FCA induced rat paw edema: When compared to the conventional and drug-treated rats, the rat paw volume of the FCA-injected control rats is noticeably larger. Rat paw oedema volume was significantly reduced by ethanolic extract administration at 200 and 400 mg/kg in comparison to the control group. The impact of the extract on arthritis produced by Freund's adjuvant model is displayed in Table 1. After 21 days, it was discovered that the ethanolic extract greatly inhibits paw thickness in a dose-dependent manner, meaning that the chronic inflammation brought on by the adjuvant causes a decrease in paw thickness. After Freund's adjuvant was added, the paw thickness was greatly reduced by standard diclofenac sodium (39.11±1.23), but it was significantly reduced by the extract at high doses. The percentage protection against a rise in paw volume was determined to be 71.56 ± 2.79% in the case of the high dose of the ethanolic extract, compared to 79.16 ± 2.68% in the case of the low dose.

Table 1: Percentage protection against increase in paw volume

Groups	Day 1	Day 7	Day 14	Day 21
Control	0.49±0.002	51.17±2.73	86.83±2.73	126.3±1.19
Standard	0.23±0.006	20.56±1.67	48.98±0.59	39.11±1.23***
Test-1 (200 mg/kg)	0.28±0.007	33.17±2.08	78.50±1.87	79.16±2.68*

Test-2 (400 mg/kg)	0.27±0.02	34.56±1.87	72.11±1.63	71.56 ± 2.79**

All the results are expressed as Mean ± SEM (n=6), for each experimental group. The statistical analysis was carried out using one way ANOVA method. Significant after analysis of variance (ANOVA) followed by Bonferroni's test. *P<0.05, **P<0.01, ***P<0.001 when compared to control group

Body weight changes: The results of this study make it abundantly evident that the degree of weight reduction and the level of joint inflammation are closely related. When comparing the control group to the standard and both test-treated groups, it was discovered that the standard group's rats weighed the most, at 178.75 ± 2.45 grammes. Both the standard medicine and the alcoholic extract at high and low doses considerably increased the animal's body weight in comparison to the control group, which was 165.45±2.11 gms for the low dose group and 170.8± 1.56 gms for the high dose group, as shown in Table 2. The rats' body weight increased in response to the extract in a dose-dependent manner.

Table 2: Body weight (grams)

Treatment days	Control	Standard	Test-1 (200 mg/kg)	Test-2 (400 mg/kg)
1	151.8±1.07	151.5±1.25	152.0±1.57	151.7±1.62
7	154.0±1.00	159.0±1.67	156.8±2.98	157.8±1.85
14	158.8±0.65	169.7±0.88	164.0±0.59	166.2±1.68
21	162.5±1.56	178.75±2.45***	165.45±2.11 *	170.8± 1.56**

All the results are expressed as Mean ± SEM (n=6), for each experimental group. The statistical analysis was carried out using one way ANOVA method. Significant after analysis of variance (ANOVA) followed by Bonferroni's test. *P<0.05, **P<0.01, ***P<0.001 when compared to control group

Biochemical estimation: All rats with arthritis had higher levels of SGPT, SGOT, and ALP than control rats due to adjuvant-induced inflammation. Following extract therapy, group 3 and group 4 animals' levels of these enzymes were considerably lower than those of the control group. More biochemical alterations were avoided by the diclofenac sodium (15 mg/kg) therapy than by the plant's ethanolic extract. Every group's bilirubin, SGOT, SGPT, and ALP (Ka) levels were assessed and contrasted with one another. In comparison to the extract-treated group, whose levels were 87.11±1.28, 93.11±1.67, and 79.45±2.67, 90.11±1.67 IU/L for the low dose and high dose groups, respectively, the standard group's SGOT and SGPT levels were the lowest, measuring 62.11±1.43 and 74.45±2.66 IU/L, respectively. Its anti-arthritic efficacy was demonstrated by the fact that treated groups were able to lower their SGOT and SGPT levels more effectively than the control group (144.2±1.64 and 130.7±2.76). Likewise, additional parameters such as bilirubin and ALP (Ka) were also examined, and Table 3 displays the corresponding findings.

Table 3: Liver function tests after treatment

Groups	SGPT (IU/L)	SGOT (IU/L)	ALP (Ka)	Bilirubin
Control	144.2±1.64	130.7±2.76	40.12±2.32	4.8±1.27
Standard	62.11±1.43*	74.45±2.66*	22.54±0.77*	1.83±0.043*

Test-1 (200 mg/kg)	87.11±1.28*	93.11±1.67*	26.17±0.47*	3.50±0.42
Test-2 (400 mg/kg)	79.45±2.67*	90.11±1.67*	24.67±0.33*	2.00±0.25*

All the results are expressed as Mean ± SEM (n=6), for each experimental group. The statistical analysis was carried out using one way ANOVA method. Significant after analysis of variance (ANOVA) followed by Bonferroni's test. *P<0.05, **P<0.01, ***P<0.001 when compared to control group

Radiological study: The following observation is illustrated by the radiographs of the rat joints in the FCA-induced arthritic rat model in Figure 1. In addition to bone loss and joint space constriction, the arthritic control rats also displayed soft tissue oedema. Groups treated with EEFE have shown decreased soft tissue swelling and joint space constriction, preventing this bony damage. The group treated with Diclofenac did not exhibit bone damage. During the development stage, the EEFE revealed a slight joint inflammation.

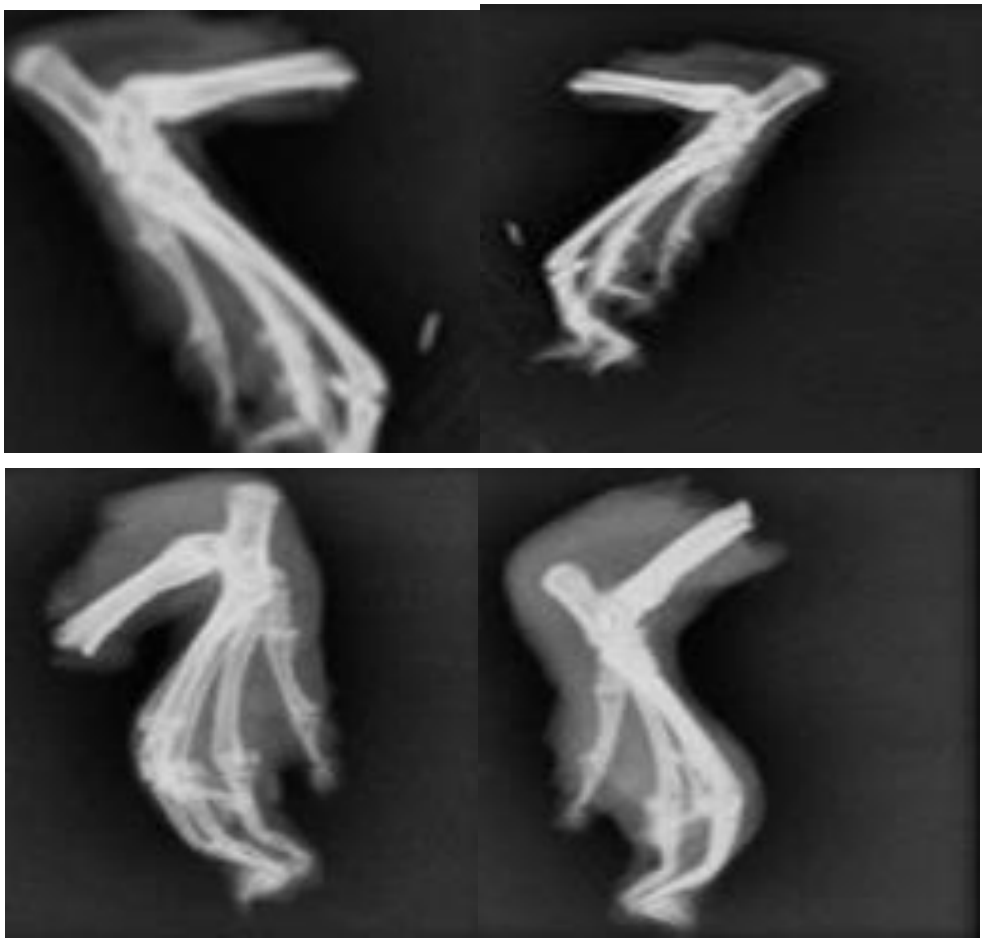

Figure 2. Radiographs of hind legs in adjuvant-induced arthritic rats. (A) Group I normal control; (B) group II positive control; (C) group III EEFE-200; (D) group IV EEFE-400

DISCUSSION

Paw swelling measurement appears to be a rapid, easy, and sensitive method for determining the level of inflammation and evaluating the therapeutic benefits of Rats in an adjuvant-induced arthritis model experienced chronic swelling in several joints, which is similar to human rheumatoid illness. This swelling was caused by inflammatory cells, joint cartilage erosion, bone deterioration, and remodelling. In the end, these inflammatory alterations cause the afflicted animal's joint integrity and functions to be totally destroyed. Furthermore, the CFA-administered rats showed soft tissue swelling around the ankle joints when arthritis occurred; this was considered to be oedema of the particular tissues.[32] An excellent and straightforward method to gauge the target drug's anti-arthritic activity is to test the levels of bilirubin, SGOT, SGPT, and ALP. In rats with arthritis, these enzymes' activity were markedly elevated. These are good markers of deterioration of the liver and kidneys, which are also thought to be characteristics of adjuvant arthritis.[33]

In our investigation, Ficus elastica's ethanolic extract demonstrated a noteworthy anti-arthritic effect that was dose dependent. In this study, we demonstrated that an ethanolic extract of F. elastica might effectively slow the development of rheumatoid arthritis in rats receiving treatment. However, both the acute and chronic phases of paw swelling were greatly reduced by normal medication and alcoholic extract. This may be because Freund's adjuvant is induced, which suppresses the production of inflammatory mediators. [34] The presence of alkaloids and flavonoids can be linked to the suppression of inflammation and antioxidant activity, even though the precise mechanism of this suppression is unknown. Radiographic alterations in RA patients are helpful diagnostic indicators that show how severe the illness is. While major radiographic alterations such as bone erosions and narrowing of joint spaces can only be seen in the advanced stages of rheumatoid arthritis, soft tissue swelling is the first radiological indicator. [35]

4. CONCLUSIONS

Based on the current experimental results of the pharmacological and biochemical parameters observed in the current investigation, it is concluded that the alcoholic extract of Ficus elastica has potentially useful anti-arthritic activity at doses of 200 mg/kg and 400 mg/kg because it effectively reduces inflammation in rats with an adjuvant-induced arthritic model. The medication is a promising plant-based anti-arthritic agent for the management of inflammatory conditions. To determine the active phytoconstituent causing the antiarthritic action, more research is needed. Future research on the molecular mechanism behind the antiarthritic properties of Ficus elastica plant extracts may help create an alternative treatment for rheumatoid arthritis.

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