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Antiarthritic activity of different plant extracts of *Ficus religiosa* stem bark in complete Freund's adjuvant-induced arthritis in rats

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ABSTRACT

Aim: The present study was carried out to evaluate the antiarthritic activity of different plant extracts of *Ficus religiosa* bark on complete Freund's adjuvant-induced arthritis in rats. **Method:** The different plant extracts were administered orally at a dose of 200 and 400 mg/kg. Arthritis was assessed by various parameters such as paw volume assessment, paw thickness assessment, arthritic scoring, and change in body weight on day 0, 7, 14, 21, and 28. Serum parameters such as serum glutamic oxaloacetic transaminase, serum glutamate-pyruvate transaminase, urea, and creatinine level were also estimated for assessing the antiarthritic potential of different extracts of *F. religiosa*. **Results:** The results of the current investigation concluded that methanol extract possesses a significant antiarthritic activity against adjuvant-induced arthritis model and justifying its therapeutic role in arthritic condition. **Conclusion:** It can be concluded from the study that the observed antiarthritic activity may be due to the presence of phytoconstituents such as flavonoids and terpenoids.

Key words: Complete Freund's adjuvant, *Ficus religiosa*, rheumatoid arthritis

INTRODUCTION

Rheumatoid arthritis (RA) is a non-specific multifactorial chronic, autoimmune disorder with unknown etiology. RA is an autoimmune inflammatory disease that leads to stiff and swollen joints. RA is characterized by its chronic, symmetrical, and erosive synovitis of peripheral joints.[1] A modified definition of RA is referred to as the American College of Rheumatology (ACR), 1987, revised criteria for the classification of RA was published in 1988. These criteria distinguish RA from other rheumatic conditions, with a specificity of 89% and sensitivity between 91% and 94%.[2] The symptoms of RA develop slowly and gradually and differ among patients. Before the typical articular symptoms appear, some can have flu-like symptom such as fever, tiredness, and weight loss.[3]

Ficus religiosa Linn. commonly known as "Peepal tree" belongs to the family (Moraceae). It is a large widely branched tree with leathery, heart-shaped, long tipped leaves on long slender petioles, and purple fruits growing in pairs. The plant was reported to have wide spectrum of activities such as antibacterial,[4] antidiabetic,[5] antimicrobial,[6] antiulcer,[7] analgesic,[8] and antiamnesic activity.[9]

F. religiosa plant has traditional claim for use in arthritic disorder. No pharmacological study has been carried out on evaluation of its antiarthritic activity on stem bark. Hence, the present study was carried out to evaluate antiarthritic effect of different plant extracts of *F. religiosa* bark in complete Freund's adjuvant (CFA)-induced arthritis in rat.

MATERIALS AND METHODS

Collection and Authentication of Plant Material

Fresh bark of *F. religiosa* was collected and certified from organic botanical garden of Kurukshetra University, India, during March. The voucher specimens were identified by a taxonomist, by Dr. B. D. Vashist, Department of Botany, Kurukshetra University, Kurukshetra, with reference no. KUK/BOT/IPS 32. The voucher specimens KUK/BOT/IPS 32 were deposited at the Department of Pharmaceutical Sciences, Kurukshetra University, Haryana, India, for future reference.

Preparation of Bark Extract

The plant material was washed and rinsed with tap water and dried in shade. The dried material was subjected to successive extraction using petroleum ether (PE), chloroform, ethyl acetate (EA), methanol, and water in Soxhlet apparatus, and resultant filtrate was concentrated under reduced pressure by rotary evaporator. A semisolid paste obtained by this process was stored in refrigerator throughout the study.

Preliminary Phytochemical Studies

Preliminary qualitative phytochemical screening was done for the presence of different group of chemicals, i.e., terpenoids, alkaloids, flavonoids, saponins, tannins, sterols, carbohydrates, and glycosides.[10]

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Animals

Wistar albino rats in adult size of either sex in weight ranging from 150 to 220 g were obtained from the Institutional Animal Ethics Committee of the Department of Pharmaceutical Sciences and Technology, Faculty of Medical Sciences and Health, Gurukul Kangri Vishwavidyalaya, Haridwar, under standard environmental conditions, the animals were allowed to acclimatize. The animals were kept in the animal house. They were kept in groups and each group consisted of six animals. Each group was kept in clean polyacrylic cages. It was maintained for 12 h day and light cycles at an average of ambient temperature of 25°C ± 2°C and 60% ± 10% relative humidity. All the animals had free access to standard pellet diet and water during the exposure of treatment. The experimental protocol was approved by the Institutional Animal Ethics Committee, Gurukul Kangri Vishwavidyalaya vide approval number GKV/AHF/06/2018.

Acute Toxicity Studies

Acute oral toxicity was carried out by according to the guidelines set by CPCSEA. Acute oral toxicity studies were carried out using female Wistar rats (150–220 g). The temperature in the experimental room was around 25°C. Lighting was natural that is 12 h darkness and 12 h light. The conventional laboratory diet was fed with adequate supply of drinking water. The animals were randomly selected marked to permit individual identification and kept in polypropylene cages for 1 week before dosing to allow their acclimatization to laboratory condition. The substance was tested using a stepwise procedure, each step using six animals of each dose.

Rats were used for acute toxicity studies to determine LD50 of different extracts of the plant. The animals are weighed and test substances were administered. Each extract at different doses in increasing order, i.e., 100, 200, 500, 1000, and 2000 mg/kg was administered orally to rats.

Observations were made during the first 4 h after the drug administration to notice the changes in skin, eye, mucous membrane, convulsions, sedation, and hypothermia. These studies of different extracts showed no abnormal behavior, and it was found safe up to 2000 mg/kg.[11]

Grouping of Animals

The animals are divided into 13 groups of six animals each. Each extract was dissolved in normal saline and triturated with 2% tween 80 to form an emulsion.

Table 1: Paw volume of different groups during the treatment

Group	Dose (P.O.)	Paw volume (ml) (Mean±SEM) on				
		0th day	7th day	14th day	21st day	28th day
Normal control	-	1.42±0.86	1.42±0.86	1.42±0.86	1.42±0.86	1.42±0.86
Diseases control	0.1 ml CFA (intra peritoneal)	2.21±0.47	2.43±0.65	2.45±0.74	2.48±0.74	2.55±0.74
Standard (Piroxicam)	10 mg/kg	2.18±0.50	2.25±0.44***	1.30±0.32***	1.23±0.3***	0.96±0.32**
PE extract	200 mg/kg	2.21±0.54	2.28±0.28	1.69±0.50*	1.25±0.32*	1.72±0.32
PE extract	400 mg/kg	2.20±0.24	2.27±0.74	1.68±1.62*	1.26±1.62*	1.62±1.62**
Chloroform extract	200 mg/kg	2.14±0.19	2.32±0.61	1.47±0.18**	1.44±0.18**	1.41±0.18
Chloroform extract	400 mg/kg	2.15±0.11	2.31±0.83	1.28±0.66**	1.29±0.66***	1.24±0.66**
EA extract	200 mg/kg	2.19±0.86	2.29±0.59	1.68±0.17**	1.65±0.17**	1.62±0.17
EA extract	400 mg/kg	2.10±0.25	2.39±0.28	1.55±0.65**	1.52±0.65**	1.51±0.65**
Methanol extract	200 mg/kg	2.19±0.45	2.23±0.78**	1.42±0.23***	1.41±0.23***	1.39±0.23**
Methanol extract	400 mg/kg	2.15±0.88	2.29±0.23**	1.25±0.12***	1.27±0.12***	0.99±0.12**
Aqueous extract	200 mg/kg	2.18±0.34	2.32±0.28	1.46±0.86	1.44±0.86**	1.42±0.86
Aqueous extract	400 mg/kg	2.20±0.16	2.36±0.85	1.34±0.21	1. 31±0.21**	1.3±0.21

The values are expressed as mean±SEM. All statistical analyses were performed by Dunnett's multiple comparison tests using GraphPad Instat. *P≤0.05, **P≤0.01, and ***P≤0.001 were considered statistically significant. SEM: Standard error of the mean, CFA: Complete Freund's adjuvant, PE: Petroleum ether, EA: Ethyl acetate

Table 2: Paw thickness of different groups during the treatment

Group	Dose (P.O.)	Paw thickness (cm) (Mean±SEM) on				
		0th day	7th day	14th day	21st day	28th day
Normal control	-	0.27±0.04	0.27±0.04	0.27±0.04	0.27±0.04	0.27±0.04
Diseases control	0.1 ml CFA (intra peritoneal)	0.31±0.04	2.125±0.04	2.225±0.08	2.91±0.04	3.27±0.04
Standard (Piroxicam)	10 mg/kg	0.32±0.04	1.125±0.04***	0.62±0.08***	0.45±0.04***	0.41±0.04**
PE extract	200 mg/kg	0.32±0.02	1.2±0.07	1.1±0.07**	1.1±0.07**	0.92±0.04
PE extract	400 mg/kg	0.27±0.04	1.12±0.04	0.97±0.04**	0.9±0.07**	0.55±0.06**
Chloroform extract	200 mg/kg	0.31±0.02	1.3±0.07	1.2±0.09**	0.7±0.03***	0.62±0.04
Chloroform extract	400 mg/kg	0.27±0.04	1.12±0.04	0.77±0.04**	0.6±0.06***	0.44±0.06**
EA extract	200 mg/kg	0.33±0.07	1.31±0.05	1.26±0.07**	0.52±0.05**	0.59±0.05
EA extract	400 mg/kg	1.11±0.06	1.30±0.07	1.29±0.07**	1.16±0.04**	0.63±0.05**
Methanol extract	200 mg/kg	1.21±1.11	1.24±0.06**	0.79±0060***	0.76±0.08***	0.42±0.80**
Methanol extract	400 mg/kg	1.39±0.05	1.90±0.06**	0.85±0.03***	0.74±0.04***	0.44±0.07**
Aqueous extract	200 mg/kg	1.36±0.03	1.96±0.07	1.23±0.05	0.91±0.06**	0.69±0.06
Aqueous extract	400 mg/kg	1.35±0.05	1.53±0.04	1.25±0.06	1.82±0.07**	0.60±0.05

The values are expressed as mean±SEM. All statistical analyses were performed by Dunnett's multiple comparison tests using GraphPad Instat. *P≤0.05, **P≤0.01, and ***P≤0.001 were considered statistically significant. SEM: Standard error of the mean, CFA: Complete Freund's adjuvant, PE: Petroleum ether, EA: Ethyl acetate

The animal groups are as follows:
Group I: Normal control (normal saline)
Group II: Disease control (0.1 ml CFA 6 mg/ml in tween)
Group III: Standard group (piroxicam 10 mg/kg + CFA)
Group IV: PE extract 200 mg/kg
Group V: PE extract 400 mg/kg
Group VI: Chloroform extract 200 mg/kg
Group VII: Chloroform extract 400 mg/kg
Group VIII: EA extract 200 mg/kg
Group IX: EA extract 400 mg/kg
Group X: Methanol extract 200 mg/kg
Group XI: Methanol extract 400 mg/kg
Group XII: Aqueous extract 200 mg/kg
Group XIII: Aqueous extract 400 mg/kg

Induction of Arthritis

Adjuvant-induced arthritis in rats

Arthritis was induced in rats by the intraperitoneal injection of 0.1 ml of CFA in the left hind paw. The CFA contains heat-killed *Mycobacterium tuberculosis* in sterile paraffin oil (10 mg/ml). The arthritis develops within 14 days from the day of administration of CFA, i.e., from the day of induction of arthritis. Oral feeding of rats with that of different extracts and standard drug was, therefore, started from the 0th day to 28^{h} day of initiation of arthritic condition. The paw volume, paw thickness, and body weight of all the animal groups were measured using a plethysmometer, Vernier caliper, and weighing balance, respectively.[12] The rats were anesthetized under light ether anesthesia, and blood was collected by retro-orbital puncture for estimation of serum parameter such as serum glutamic oxaloacetic transaminase (SGOT), serum glutamate-pyruvate transaminase (SGPT), urea, and creatinine using various diagnostic kits.[13]

Assessment of Arthritis

Measurement of paw volume

The severity of adjuvant arthritis was quantified by measuring the volume of the hind paw using plethysmometer. Paw volume (ml) was measured at 0 day and thereafter 7, 14, 21, and 28 days of CFA postinoculation. Data were expressed as the increase in paw volume with respect to the initial day.[14]

Table 3: Effect of extracts on body weight in CFA-induced arthritis rat

Group	Dose (P.O.)	Mean body weight in a g at initial day	Mean body weight in a g on day 28	Mean difference body weight in g (±SEM)
Normal control	-	177.5±3.22	211±3.14	33.75±3.14
Diseases control	0.1 ml CFA (intraperitoneal)	176.3±2.39	185±2.88	8.75±1.25
Standard (Piroxicam)	10 mg/kg	176.3±3.75	200±3.53	23.75±4.2
PE extract	200 mg/kg	180±4.08	193.8±2.39	13.77±2.39
PE extract	400 mg/kg	178.8±1.25	201.3±3.14	22.5±3.22
Chloroform extract	200 mg/kg	179±4.08	190.8±2.39	11.77±1.69
Chloroform extract	400 mg/kg	177.3±1.25	200.3±3.14	23.0±3.22
EA extract	200 mg/kg	109.2±1.08	199.2±3.12	2.00±2.14
EA extract	400 mg/kg	181.3±1.11	196.3±2.78	15.0±2.56
Methanol extract	200 mg/kg	169.2±1.21	186.4±3.19	17.2±3.19
Methanol extract	400 mg/kg	176.3±2.11	188.5±2.39	12.2±2.41
Aqueous extract	200 mg/kg	177.5±3.21	192.3±3.22	14.8±3.22
Aqueous extract	400 mg/kg	180±4.08	199.4±4.21	19.4±4.20

SEM: Standard error of the mean, CFA: Complete Freund's adjuvant, PE: Petroleum ether, EA: Ethyl acetate

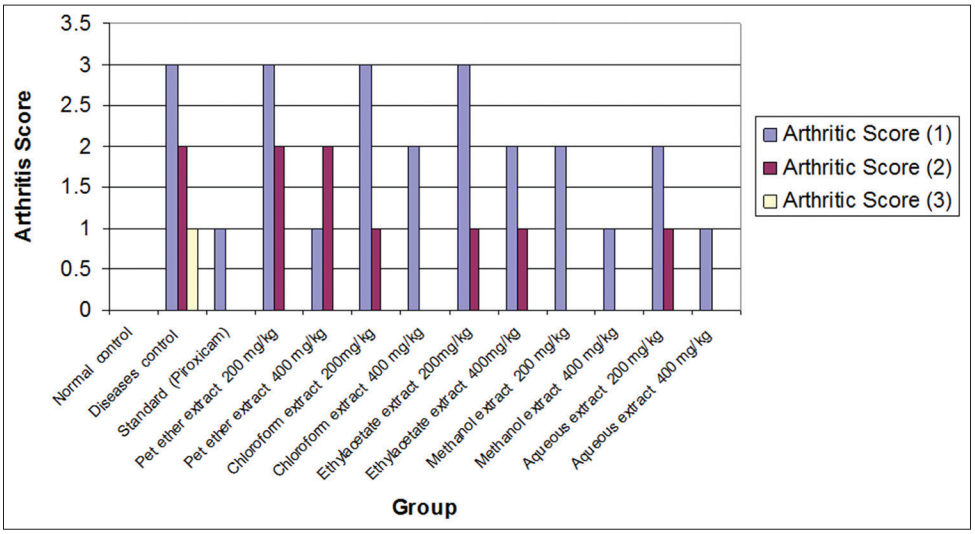

Figure 1: Graph showing arthritis score of different groups during the treatment

Table 4: Arthritic score of different groups during the treatment

Group	Dose (P.O.)	Arthritic score
Normal control	-	0
Diseases control	0.1 ml CFA (Intraperitoneal)	3+2 + 1
Standard (Piroxicam)	10 mg/kg	1
PE extract	200 mg/kg	3+2
PE extract	400 mg/kg	1+2
Chloroform extract	200 mg/kg	3+1
Chloroform extract	400 mg/kg	2
EA extract	200 mg/kg	3+1
EA extract	400 mg/kg	2+1
Methanol extract	200 mg/kg	2
Methanol extract	400 mg/kg	1
Aqueous extract	200 mg/kg	2+1
Aqueous extract	400 mg/kg	1

PE: Petroleum ether, EA: Ethyl acetate

Table 5: Effect of different extracts of *Ficus religiosa* on liver function test in CFA-induced arthritis rats

Group	Dose (P.O.)	On 28th day (Mean±SEM)	
		SGOT (U/L)	SGPT (U/L)
Normal control	-	111.2±1.06	45.3±1.18
Diseases control	0.1 ml CFA (intra peritoneal)	142.1±1.27	48.5±1.55
Standard	10 mg/kg	102.8±1.50	42.4±1.24
PE extract	200 mg/kg	120.1±1.54	44.8±1.28
PE extract	400 mg/kg	114.2±1.24	44.7±1.14
Chloroform extract	200 mg/kg	113.4±1.90	48.2±1.11
Chloroform extract	400 mg/kg	110.5±1.11	49.9±1.83
EA extract	200 mg/kg	119.9±1.26	47.9±1.19
EA extract	400 mg/kg	109.1±1.25	44.4±1.28
Methanol extract	200 mg/kg	112.9±1.51	45.3±1.78
Methanol extract	400 mg/kg	107.5±1.08*	43.6±1.23*
Aqueous extract	200 mg/kg	113.8±1.34	46.2±1.28
Aqueous extract	400 mg/kg	112.2±1.16	48.1±1.25

*All values are shown as mean±SEM and *n*=6. SEM: Standard error of the mean, CFA: Complete Freund's adjuvant, PE: Petroleum ether, EA: Ethyl acetate, SGOT: Serum glutamic oxaloacetic transaminase, SGPT: Serum glutamate-pyruvate transaminase

Measurement of paw thickness

At chosen time points, paw thickness (cm) was measured using Vernier caliper at 0 day and thereafter 7, 14, 21, and 28 days of CFA postinoculation. Data were expressed as the increase in paw volume with respect to the initial day.[15]

Arthritic scoring

Experimental animals were investigated on a daily basis for signs of the arthritic severity through well-established extensively used scoring system. Severity of paws was graded on the basis of the swelling and erythema using 5-point scale scoring system. In this scale, no sign of diseases (non-toxic), signs involving the wrist/ankle, signs involving the ankle, plus tarsal of the hind paw and/or wrist plus carpals of the forepaw, signs extending to the metatarsals or metacarpals, severe disease involving the entire hind, or forepaw were assigned as 0–4 scores.[16]

Change in body weight

To observe the effects of given formulation on the body weights of animals, body weight was recorded initially and on the 28th day. Body weights were observed using a single pan weighing balance. The records were evaluated for the effects of given treatment on the body weight of animals.

Statistical Evaluations

Statistical comparison was performed using multiple comparisons versus control group followed by Dunnett's test. All statistical analyses were performed using ANOVA analysis. $P < 0.05$, $P < 0.01$, and $P < 0.001$ were considered statistically significant.

RESULTS

RA is a chronic autoimmune inflammatory polyarticular joint disease, and it affects several parts of joints including cartilage, synovium, tendon, and muscles.[17,18] In the present study, Wistar rats were selected to induce arthritis because rats develop a chronic swelling in multiple joints. CFA-induced models are extensively used to study the pathogenesis of RA for testing therapeutics. These experimental models share several clinical and pathological features with RA. *F. religiosa* significantly reduces the signs of pain, inflammation, and other symptoms of RA. Therefore, further, the antiarthritic activity of *F. religiosa* was evaluated by CFA-induced arthritis in rats.

From the acute oral toxicity study, it was found that different plant extracts of *F. religiosa* at different dose levels were safe up to 2000 mg/kg. Therefore, we have taken 400 mg/kg as the therapeutic dose and made variations by taking 200 mg/kg as lower dose and 400 mg/kg as higher dose for pharmacological evaluation.

Induction of arthritis in all groups except normal group had shown increase in paw volume. Later, the animals were treated with standard drug, 200 mg and 400 mg of different extracts of plant. Until the 7th day, there was an increase in paw volume, but later, it was observed that paw volume reduction was significant in all groups [Table 1]. Paw thickness was increased until the 7th day after the induction of CFA in all groups. Later, the animals had shown the gradual decrease in paw thickness except in normal group as shown in Table 2.

In arthritis individuals, there is decrease in body weight. Here, in Table 3, the significant change in mean body weight between the 0 day and 28th day of animals of different groups during the treatment is shown.

The arthritis morphological feature of like redness, swelling, and erythema was monitored by set visual criteria as follows: 0 = No signs of arthritis, 1 = swelling/redness in only one joint, 2 = swelling/redness in more than one joint, 3 = swelling/redness in entire paw, and 4 = severe swelling of entire paw with deformity and/or ankylosis.

As we can see from Table 4 and Figure 1 that the individuals affected with arthritis have a higher arthritic score, and the individuals treated with methanolic extract have the least arthritic score.

The SGOT, SGPT, urea, and creatinine levels in blood are generally

Table 6: Effect of different extracts of *Ficus religiosa* on kidney function test in CFA-induced arthritis rats

Group	Dose (P.O.)	On 28th day (Mean±SEM)	
		Urea (mg/dl)	Creatinine (mg/dl)
Normal control	-	35.2±1.09	0.94±0.48
Diseases control	0.1 ml CFA (intra peritoneal)	58.4±1.15	0.76±0.45
Standard	10 mg/kg	42.5±1.04	0.58±0.34
PE 200 mg/kg	200 mg/kg	46.2±1.08	0.61±0.34
PE 400 mg/kg	400 mg/kg	48.5±1.04	0.62±0.58
Chloroform 200 mg/kg	200 mg/kg	45.5±1.10	0.67±0.38
Chloroform 400 mg/kg	400 mg/kg	48.6±1.13	0.66±0.75
EA 200 mg/kg	200 mg/kg	44.6±1.09	0.66±0.45
EA 400 mg/kg	400 mg/kg	45.2±1.18	0.69±0.64
Methanol 200 mg/kg	200 mg/kg	45.6±1.08	0.65±0.68
Methanol 400 mg/kg	400 mg/kg	44.1±1.03*	0.60±0.85*
Aqueous 200 mg/kg	200 mg/kg	46.6±1.18	0.68±0.38
Aqueous 400 mg/kg	400 mg/kg	47.2±1.15	0.64±0.68

*All values are shown as mean±SEM and *n*=6. SEM: Standard error of the mean, CFA: Complete Freund's adjuvant, PE: Petroleum ether, EA: Ethyl acetate

lower in normal individuals, and their levels are increased in arthritic condition. From the study, it was found that the groups which were treated with standard and different plant extracts showed decreased levels of these parameters [Tables 5 and 6].

DISCUSSION

The present study was carried out to see the efficiency of Indian herbal source against a chronic inflammatory disease, i.e., arthritis. In the present study, rats were selected to induce arthritis because they develop a chronic swelling in multiple joints due to accumulation of inflammatory cells, erosion of joint cartilage, and bone destruction. It has close similarities to human rheumatoid diseases.[19] The determination of paw swelling is apparently simple, sensitive, and quick procedure for evaluating the degree of inflammation and the therapeutic effects of drugs. The Freund's adjuvant model is chosen as it develops chronic swelling in multiple joints with influence of inflammatory cells with erosion of joint cartilage and bone destruction. Chronic inflammation involves the release of number of mediators such as cytokines (interleukin-1B and tumor necrosis factor-alpha), granulocyte-macrophage colony-stimulating factor, interferons, and PDGF (Platelet Derived Growth Factor). These mediators are responsible for the pain, destruction of bone, and cartilage that can lead to severe disability.[20] However, standard drug and methanolic extract of *F. religiosa* significantly suppressed the swelling of the paws and also decrease the paw volume in both acute and chronic phase which may be due to the suppression of inflammatory mediator released due to induction of Freund's adjuvant. Although the actual mechanism of suppressing inflammation is not known, it can be correlated with the presence of flavonoids and terpenoids in suppressing the inflammation. As the incidence and severity of arthritis increased, the changes in the body weights of the rats also occurred during the course of the experimental period. The increased body weight during the treatment of standard drug and plant extracts may be due to the restoration of absorption capacity of intestine. The extract also shows the effect on various serum parameters.

CONCLUSION

From the results observed it is concluded that the methanolic extract of *F. religiosa* possesses potentially useful antiarthritic activity since it gave a positive result in controlling inflammation in adjuvant-induced arthritis in rats.

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