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Original Article

Anti-arthritic Potential of Aqueous and Ethanolic Extracts of *Euphorbia helioscopia* on Adjuvant-induced Arthritis in Rats

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ABSTRACT

Background: *Euphorbia helioscopia* is of the family Euphorbiaceae, owning various pharmacological properties like anti-inflammatory activity. Rheumatoid Arthritis (RA) is a chronic-autoimmune systemic disease that can be characterized by cartilage degradation, synovial hyperplasia, inflammation, and joint damage. **Objectives:** To assess the anti-arthritic activity of aqueous and ethanolic extracts of *Euphorbia helioscopia*. **Materials and Methods:** Adjuvant-induced arthritis (AIA) method was followed for the evaluation. Complete Freund's adjuvant (CFA) was used to induce arthritis in female Wistar rats. Aqueous and ethanolic extracts (300, 150, and 75 mg/kg/day) of aerial parts of *Euphorbia helioscopia* were given orally to Wistar rats. **Results:** Both the extracts showed significant anti-arthritic activity in a dose-dependent manner. However, ethanolic extract (300mg/kg) of *Euphorbia helioscopia* showed potential anti-arthritic activity among the tested extracts. **Conclusion:** From the study, it can be concluded that *Euphorbia helioscopia* possesses marked anti-arthritic activity.
Keywords: Rheumatoid arthritis, *Euphorbia helioscopia*, Adjuvant induced arthritis, Anti-inflammatory, Aqueous and ethanolic plant extracts.

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INTRODUCTION

RA is an autoimmune systemic disease that can be characterized by cartilage degradation, synovial-hyperplasia, inflammation, and joint damage. RA is the outcome of an immune reply where the body's healthy cells are attacked by its immune system, especially the synovial membrane, or synovium, triggering an inflammatory response. The disease can lead to disability, premature mortality, and decreased life quality due to bone erosion and joint deformity.[1-2] RA approximately affects about 0.24-1% of the population and is more common in women in comparison to men.[3]

Till now there has been no permanent cure for RA. However, there are treatments to manage it. Currently, disease-modifying anti-rheumatic drugs (DMARDs), nonsteroidal anti-inflammatory drugs (NSAIDs), and Steroids are all used to treat RA. Among these, DMARDs are widely and most commonly used for the treatment of RA. These can reduce or prevent joint swelling and pain, decrease acute-phase markers, reduce the progression of joint deterioration, and enhance overall functionality.[4] Most commonly used DMARDs in RA include methotrexate (MTX), leflunomide (LF) sulfasalazine (SSZ), cyclosporine, etanercept, and infliximab. Among these, Methotrexate is recommended as a first-line treatment drug for RA.[5] NSAIDs are drugs with anti-pyretic, anti-inflammatory, and analgesic effects. These are very effective in pain and stiffness management at RA onset. The cyclooxygenase (COX) enzymes are the primary target of NSAIDs.[6] Glucocorticoids (GCs) are potent drugs with anti-inflammatory and immune-suppressive properties belonging to the class of steroid hormones that have been widely used in the treatment of RA. However, all of these drugs are linked with a considerable amount of toxicity especially with long-term usage, which makes careful monitoring of patients essential. Major toxicity comprises gastrointestinal problems, oral ulceration, hepatotoxicity, nephrotoxicity, and hematological toxicity.[7-8] Therefore, due to various side effects that tail long-term usage of conventional therapy, alternative therapies are constantly being researched.

The area of arthritis research has significantly progressed in the direction of herbal medicine, that is thought to be both safe and effective in alleviating the pain accompanying the disease. Medicinal herbs have been shown to be effective in the treatment of RA.[9] Medicinal plants can be used to treat RA in a variety of ways, and a number of medicinal plants are now being studied in the hope of developing novel drugs.[10] Anti-arthritic properties have been reported in several medicinal plants, including *Aloe barbadensis, Withania somnifera* Linn., and *Zingiber officinale*.[11] Thus, it is practical to exploit the

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curative effectiveness and possible adverse effect, of these herbal plants for providing new and better treatment alternatives with minimum or no side effects.[10]

The current study tried to evaluate the therapeutic potential of *Euphorbia helioscopioa* in the management of RA.

MATERIALS AND METHODS

Chemicals and Reagents

Ethanol and aqueous extracts of *Euphorbia helioscopia* were obtained from the cold extraction of the aerial parts of *Euphorbia helioscopia*. Methotrexate (purity≥98%), Complete Freund's adjuvant (CFA) was purchased from Sigma-Aldrich (St Louis, MO, USA). All other chemicals and reagents used were of research-grade.

Dose Selection and Dose Formulation

The selection of the effective dose of the ethanolic and aqueous extracts (300mg/kg) of *Euphorbia helioscopia* was done according to Uzma *et al.*[12] Besides the selected dose, a medium and a lower dose were also chosen. The dose was given orally to rats in the form of suspension prepared with the help of 2% gum acacia.

Experimental Animals

From the Animal House of Indian Institute of Integrative Medicine, Jammu, female Albino Wistar rats (6-8 weeks old, weighing 120-170g) were acquired and used for experimentation (IAEC approval No: 228/78/2/2021). The animals were kept in polypropylene cages. Standard environmental conditions of light-dark cycles, temperature and humidity were maintained (a 12:12 hr, 25 ± 1°C and 55 ± 5%, respectively) and animals were fed with a standard pellet diet (Ashirwad Feed, Chandigarh, India) and water *ad libitum*. Animal experimentation were permitted by the Institutional Animal Ethics Committee and followed the ethical guidelines of the International Association for the Study of Pain.

Adjuvant Induced Arthritis Model (AIA) Induction of Arthritis

50 µl of CFA containing heat-killed Mycobacterium tuberculosis (5 mg/ml) were injected subcutaneously into the footpad region of rats left hind paw. Test substances were introduced into gastric region of rats by oral gavaging for 14 days from day 0 (one day before disease induction). The paw volume changes were recorded on substitute days up to 21 days and body weight was documented on 0, 7th, 14th and 21st day after the injection of CFA. On the last day, blood samples were collected from each rat into tubes with and without anticoagulant. Finally, at the end of the experiment that is on the 21st day, to dissect the spleen out, rats were euthanized by decapitation.[13]

Experimental Groups

Nine groups of Wistar rats, each consisting of 5 animals were formed (n = 5).

Group I-vehicle control (without treatment).

Group II-Disease control or negative control, arthritic rats.

Group III- Positive control, arthritic rats treated with Methotrexate (the standard anti-arthritic drug, 3mg/kg/weekly) orally.

Group IV-Group-V and Group-VI- Arthritic rats were administered Aqueous extract *of Euphorbia helioscopia* (300mg/kg/day), (150mg/kg/day), and (75mg/kg/day) respectively.

Group VII, Group VIII, and Group- IX arthritic rats were administered Ethanolic extract of *Euphorbia helioscopia* (300, 150, and 75 mg/kg/day).

Measurement of Bodyweight

The changes in body weight were measured with the aid of digital weighing balance on days 0, 7th, 14th, and 21st days.

$$\text{Percent change in body weight} = \frac{(\text{weight on day x} - \text{weight on day 0})}{\text{weight on day 0}} \times 100$$

Measurement of Paw Edema

The changes in paw volume of all the rats were recorded on different days (0, 7th, 14^{th,} and 21$^{st)}$ by using Digital Vernier caliper.

Measurement of Spleen size

In order to sacrifice the animals, cervical decapitation was done on the 21st day. The spleen was anatomized from the body and the organ weights were documented.

Estimation of Changes in Biochemical and Hematological Parameters

The blood was withdrawn by retro-orbital puncture and was subjected to several studies including hematological; hemoglobin (Hb), white blood cell (WBC), red blood cell (RBC), platelet count, Neutrophil count, lymph, etc. and biochemical; ALP, total triglyceride (TG), bilirubin, Uric acid, total cholesterol (TC), SGOT (serum glutamic oxaloacetic transaminase), total proteins (TP), SGPT (serum glutamic pyruvic transaminase), and total Urea.

Statistical significance

Attained data is presented as mean ± S.E.M., n = 5. One-way ANOVA and Dunnett's test were used for the calculation of statistical significance by comparing the control with the treated group.

RESULTS

Effect of aqueous and ethanolic extract of *Euphorbia helioscopia* on body weight of adjuvant-induced arthritic rats.

In the present study, after the induction of arthritic, diseased rats showed considerable weight loss as compared to the control group. Groups treated with MTX, ethanolic and aqueous extracts particularly at 300mg/kg of *Euphorbia helioscopia* showed an improved growth rate (Figure 1).

Effect of Aqueous and Ethanolic Extracts of *Euphorbia helioscopia* on Paw Size

As shown in Figure 2, the results showed a rise in paw size of rats on induction of arthritis. Groups treated with Methotrexate and Ethanol extract (300mg/kg) of *Euphorbia helioscopia* showed noteworthy inhibition of paw inflammation by 47% and 51% respectively in comparison to the diseased group. Other groups also showed significant inhibition in paw size as compared to the disease control groups.

Effect of Aqueous and Ethanolic Extracts of *Euphorbia helioscopia* on Spleen Size

The arthritic rats showed a significant upsurge in spleen size in comparison to the healthy rats. Treatment with methotrexate noticeably lowered the weight of the spleen in arthritic rats whereas, in comparison to the disease group, the extract-treated arthritic rats remarkably lessened the weight of the spleen during the treatment (Figure 3).

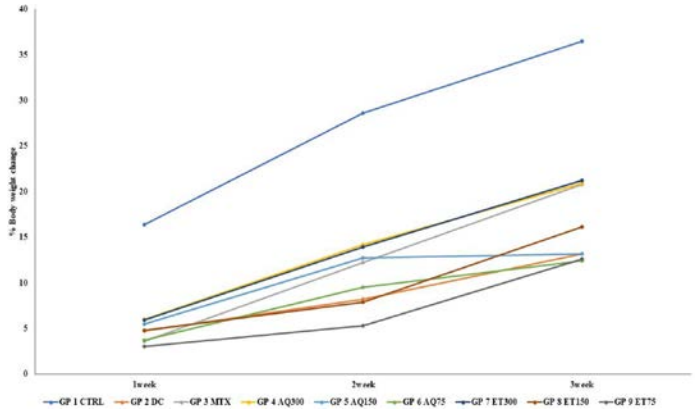

Figure 1: Dose-dependent antiarthritic effect of different extracts on the body weight with respect to standard drugs in adjuvant-induced arthritic female Wistar rats.
In this Figure GP1 = control, GP2 = diseased control, GP3 = methotrexate 3 mg/kg (twice weekly), GP4 = AQ300mg/kg, GP5 = AQ150 mg/kg, GP6AQ75mg/kg, GP7 = ET300mg/kg, and GP8=ET150 mg/kg.and GP9=ET75mg/kg.

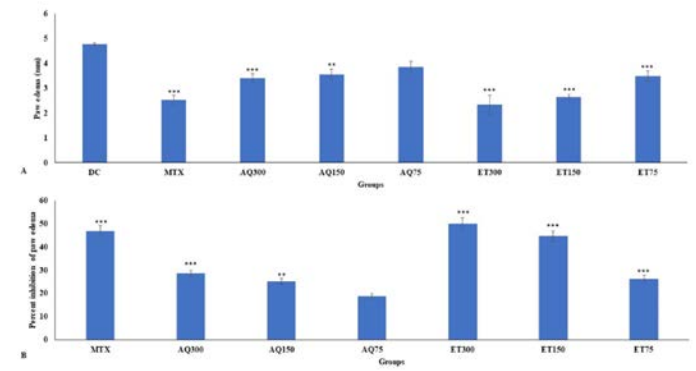

Figure 2: Graph (A) represents paw edema whereas Graph (B) represents percentage inhibition of paw edema in female Wistar rats.
Embodied values are the mean ± S.E.M. of five observations. $p^* < 0.05$, $p^{**} < 0.01$ and $p^{***} < 0.001$, treated group compared to control group (Statistical significance was assessed by one-way ANOVA followed by Dunnett's test).

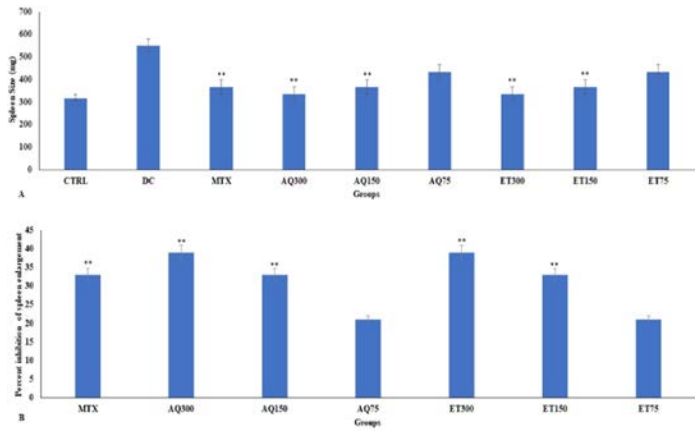

Figure 3: Graph (A) represents spleen size whereas Graph (B) represents percentage inhibition of spleen enlargement in female Wistar rats.
Embodied values are the mean ± S.E.M. of five observations. $p^* < 0.05$, $p^{**} < 0.01$ and $p^{***} < 0.001$, treated group compared to control group (Statistical significance was assessed by one-way ANOVA followed by Dunnett's test).

Effect of Aqueous and Ethanolic Extracts of *Euphorbia helioscopia* on Hematological Parameters

The experimental rats induced with FCA (Disease control group) showed decrease in RBC count, hemoglobin, HCT count, MCV, LYMPH, and platelet count and an increase in WBC count as well as Neutrophil count in comparison to the healthy rats. The group treated with Methotrexate significantly recovered the modified hematological parameter to the normal state. These parameters were also restored remarkably to the normal base values in groups treated with ethanolic and aqueous extracts. The exact details are depicted in Table 1.

Effect of aqueous and Ethanolic Extracts of *Euphorbia helioscopia* on Biochemical Parameters

A significant raise in the level of ALP, SGOT CRENZ, Triglycerides, and Uric acid was noticed in the Disease control group in comparison to normal control rats. There was also a remarkable decrease in total glucose, total cholesterol, total protein, and total Urea in the disease control group in comparison to normal rats. However, upon treatment with ethanol and aqueous extracts of *Euphorbia helioscopia* these altered parameters were brought to normal levels. The exact details are depicted in Table 2.

DISCUSSION

Inflammation itself is a valuable host response but any breakdown in the inflammatory process regulation leads to extreme tissue damage.[14] Inflammation can have acute nature or a more chronic form for instance seen in arthritis.

RA is a chronic crippling disease that involves articular inflammation and the formation of rheumatoid pannus that can initiate long-term loss of function, joint damage, and disability.[15] Treatment of RA involves Steroids, NSAIDs, and DMARDs. DMARDs being the first choice of treatment for RA are generally used to reduce disease progression and improve the functionality of joints.[4] NSAIDs are drugs with anti-inflammatory, analgesic, and antipyretic effects. These are very effective in relieving pain and stiffness at RA onset. The cyclooxygenase (COX) enzymes are the chief target of NSAIDs.[6] Glucocorticoids (GCs) are potent anti-inflammatory and immunosuppressive drugs belonging to the class of steroid hormones that have been widely used in the treatment of RA.[7-8] However, all of these current therapies are loaded with several side effects including hepatotoxicity and gastrointestinal problems. Therefore, there is always an ongoing search for better and safe therapeutics.[7] Conventional drugs are the mainstay for RA treatment. However, in response to high cost and unwanted side effects associated with conventional therapy; people are now increasingly in progress in exploring alternative therapies.[16] Frequently used alternative methods include nutritional supplements, diet modification, and herbal medicines. These alternative treatments can be used as an adjunct or as an alternative to conventional therapy or both.[17]

Nowadays, there is an increase in ongoing research for herbal medicines in the world.[18] Ayurvedic medicine, kampo, traditional chinese medicine (TCM), and homoeopathy are amongst the foremost contributors of herbal medicines. India offers a varied spectrum of medicinal plants, with about 2000 medicinal plants described in the ancient Unani, Ayurvedic, and Tibbi schools of medicine.[19] The demand for herbal medicines is growing annually (15%-25%) and according to WHO, the demand is on the verge of surge more than 5 trillion US dollars in 2050. In India, the trade of medicinal plants is valued to be approximately 1 billion US Dollars per year.[20]

Euphorbia helioscopia, known to have anti-inflammatory, anti-nociceptive, antipyretic[12] antibacterial, antiviral, antifungal,[21-23]

Table 1: Effect of different concentration of Aqueous and Ethanol extracts on blood hematological parameters change after 21 days of induction of AIA in female Wistar rats.

	GP I CTRL	GRP 2 DC	GP 3 MTX	GP 4 AQ300	GP 5 AQ150	GP 6 AQ75	GP 7 ET300	GP 8 ET150	GP 9 ET75
WBC	9.21±0.29	13.87±0.37	9.26±0.68***	9.1±0.91***	9.40±1.05**	10.72±0.68**	9.22±0.17***	10.15±0.57***	10.76±0.66**
RBC	7.2±0.159	6.5±0.25	7.1±0.26	7.01±0.19	6.4±0.22	7.04±0.024	7.11±0.06*	6.53±0.08	6.66±0.18
PLT	1127.33±63.83	1092.33±77.09	1054 ±81.67	1014.33±49.24	861.33±77.91	1007.3±68.63	810.3±49.26*	916±53.71	1163.3±44.78
NEUT	2.25±0.07	27.7±0.94	3.07±0.44***	2.76±0.39***	2.69±0.31***	3.38±0.30***	2.25±0.09***	3.43±0.42***	3.19±0.48***
HGB	13.26±0.12	10.76±0.24	12.26±0.46*	12.23±0.31**	11.9±0.20**	11.3±0.26	12±0.20**	11.9±0.20**	10.93±0.40
HCT	42.7±0.17	35.13±0.77	39.9±1.30*	38.4±0.88*	36.3±0.46	37.9±0.40*	38.1±0.57*	36.3±0.89	35.3±1.08
MCV	61.33±0.93	52.63±0.42	57.13±1.32*	55.86±1.06*	55.86±0.27**	56.16±0.66**	56.66±0.75**	55.4±0.37**	54.9±1.87
LYMPH	6.39±0.19	5 ± 0.15	6.15±1.03	7.00±0.93	5.48±0.40	4.69±0.30	6.22±0.33*	7.34±0.92	6.47±0.99
MONO	0.5±0.005	1.75±0.87	0.76±0.11	0.63±0.05	0.65±0.055	0.6±0.04	0.61±0.099	0.89±0.072	0.66±0.15
EO	0.15±0.026	1.11±0.41	0.26±0.07	0.21±0.11	0.61±0.39	0.60±0.04	0.82±0.36	1±0.45	0.24±0.15
BASO	0.01±0	0.1±0	0.01±0	0.01±0	0.01±0	0.01±0	0.01±0	0.01±0	0.01±0

Attained values are the mean ± S.E.M. of five observations. p** < 0.01, and p*** < 0.001 treated group compared to control group (Statistical significance was assessed by one-way ANOVA followed by Dunnett's test).

Table 2: Effect of different concentration of Aqueous and Ethanol extracts on change in biochemical parameters after 21 days AIA induction in female Wistar rats.

	GP I CTRL	GRP 2 DC	GP 3 MTX	GP 4 AQ300	GP 5 AQ 150	GP 6 AQ75	GP 7 ET300	GP 8 ET150	GP 9 ET75
ALP	618.33 ± 25.95	724.3±11.05	701.33±25.70	629.33±14.85***	651.33±16.33**	678±36.07	621.66±5.48***	632±14.46***	651.33±17.89**
BIT	0.07±0.01	0.07±0.01	0.06+0.00	0.07±0.01	0.07±0.01	0.07±0.01	0.07±0.01	0.08±0.005	0.07±0.00
CRENZ	0.07±0.01	1.35±0.15	0.81+0.02**	0.73±0.09**	0.79±0.05**	0.68±0.11**	0.78±0.04**	0.69±0.01**	0.73±0.06**
GLU	124.4±5.52	100.9±3.61	125.4+4.01**	116.7±0.14**	118.2±2.16**	111.8±2.63*	125.6±3.99**	111.56±0.92*	115.4±7.82
TRIG	27.66±2.32	32.13±1.27	30.9+1.10	3.9±3.04***	33.33±4.64	31.8±4.55	24.66±1.20**	43.86±1.64***	25.33±3.61
CHOL	84.33±1.85	78.66±0.66	91.66+3.52**	84±5.03	87±5	85.6±2.60*	93 ± 5.03*	89.33±0.66***	86.33±8.21
UA	2.4±0.17	5.6±0.58	4.2+0.75	3.7±0.5*	4.3±0.61	3.5±0.26*	2.9±0.37**	2.9±0.38**	4.8±0.41
PRO	7.08±0.18	6.74±0.04	7.39+0.17**	7.25±0.05***	7.21±0.05***	7.38±0.21*	7.43±0.23*	7.21±0.077***	7.40±0.145**
SGOT 1	278.2±8.15	234.2±14.0	317.8+6.10***	283.06±8.09*	271.36±2.82*	270.56±14.14	274.83±0.44*	264.03±4.70	203±4.66
SGPT 1	146.4±3.63	112.06±2.10	138.4+6.5**	120.2±3.73	149.6±37.69	141.1±7.70**	148.9±7.41**	117.4±2.50	118.9±11.63
UREA	45.73±3.06	38.73±0.21	44.4+1.32**	36.93±1.06	39.03±0.33	36.13±1.54	42.96±0.74***	40.93±0.53**	38.06±1.34

Attained values are the mean ± S.E.M. of five observations. $p^* < 0.05$, and $p^{***} < 0.001$, the treated group compared to the diseased control group (Statistical significance was assessed by one-way ANOVA followed by Dunnett's test).

anticancer,[24] anti-allergic and anti-asthmatic,[25] antioxidant[26-27] and vasodepressor[28] properties. In this study, the AIA model was used to investigate its efficacy against RA, a chronic inflammatory disorder.

In the AIA model, there is chronic inflammation involving multiple joints with the impact of immune cells, joint cartilage erosion, and bone devastation and remodeling having close resemblances to rheumatoid disease in humans. These fluctuations eventually destroy the integrity and functionality of joints in the affected animal. Paw edema is one of the main factors that determines arthritis in the adjuvant-induced arthritis model, and it is a simple, rapid, and sensitive technique to assess the severity of inflammation and the therapeutic effect of drugs.[29-30] Ethanolic extract (300mg/kg) of *Euphorbia helioscopia* inhibited inflammation significantly in terms of paw edema by 51% when paralleled to the disease group. After induction of arthritis, the diseased control group showed decreased growth rate whereas the arthritic group treated with the ethanolic extract (300mg/kg) showed an improved growth rate, comparable to the normal control group. Ethanolic extract (300mg/kg) also succeeded in reducing the inflammation in the spleen, reverting inflammatory change in the spleen, and showing effectiveness comparable to methotrexate (3mg/kg) activity. Chronic inflammation causes change in biochemical and hematological parameters. Chiefly, WBCs, SGPT, SGOT, and ALP levels are changed due to several disease factors.[29,31] Conventional remedies like methotrexate also lead to various fluctuations in biochemical and hematological profiles of blood serum and plasma (respectively) as a result of their toxicity profiles.[32-33] In our current study, ethanolic extract (300mg/kg) effectively reestablished biochemical and hematological changes that arose after the induction of arthritis in Wistar rats.

CONCLUSION

From the results, it can be concluded that the ethanolic (300mg/kg) extract of *Euphorbia helioscopia* possesses potential anti-arthritic activity.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

RA: Rheumatoid arthritis; **DMARDs:** Disease-modifying anti-rheumatic drugs; **NSAIDs:** Non-steroidal anti-inflammatory drugs; **MTX:** Methotrexate; **LF:** Leflunomide; **SSZ:** Sulfasalazine; **COX:** Cyclooxygenase; **GCs:** Glucocorticoids; **CFA:** Complete Freund's adjuvant; **AIA:** Adjuvant induced arthritis; **CFA:** Complete freund's adjuvant; **RBCs:** Red blood cells; **WBCs:** White blood cells; **Hb:** Hemoglobin; **ALP:** Alkaline phosphatase; **TC:** Total cholesterol; **TG:** Total triglyceride; **SGOT:** Serum glutamic oxalo-acetic transaminase; **SGPT:** Serum glutamic pyruvic transaminase; **TP:** Total proteins; **TCM:** Traditional Chinese medicine.

Ethical Approval

"Any studies with human participants are not presented in the article, and an approval from IAEC has been taken before the animal's experimentation."

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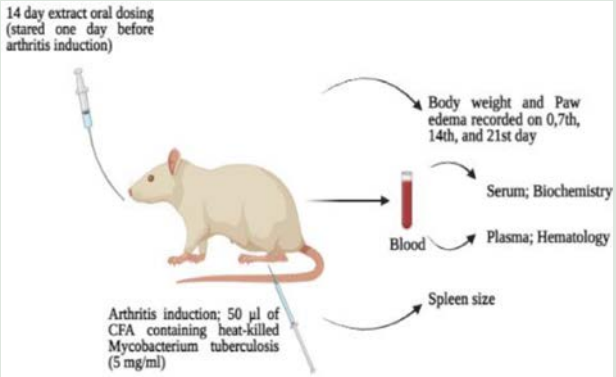
GRAPHICAL ABSTRACT

Anti-Arthritic Potential of aqueous and ethanolic extracts of *Euphorbia helioscopia* on AIA model of Wistar rat.



SUMMARY

RA is a chronic, life-threatening autoimmune disease with no permanent cure. Conventional treatment currently being used to treat RA involves various side effects besides some being costly and showing recurrence of the disease. As a result, various other therapies are being explored daily, including plant-based treatment. *Euphorbia helioscopia* is known to possess multiple pharmacological activities examined for its anti-arthritis potential against the AIA model in Wistar rats showed that the ethanolic extract (300mg/kg) of *Euphorbia helioscopia* possesses potent dose-dependent anti-arthritic activity.

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