Jatropha curcas leaves exert anti-arthritic activity on adjuvant-induced arthritis in rats

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ABSTRACT

BACKGROUND

Jatropha curcas leaves have been proven to be anti-inflammatory and antioxidant. In this study we examined the antiarthritic effects of ethanolic extract of *J. curcas* leaves using adjuvant induced arthritis (AIA) in rats.

METHODS

Male Wistar rats were divided into 6 groups (n=8), consisting of normal group (0.9% NaCl), control group (complete Freund's adjuvant/CFA), (1 mg/ml), sodium diclofenac group at a dose of 6.75 mg/kg (p.o), ethanolic extract of *J.curcas* groups at doses of 150 mg/kg (p.o), 300 mg/kg (p.o) and 600 mg/kg (p.o). Each group was induced by 0.2 ml CFA on day 1 and a booster injection on day 5. Extracts of *J. curcas* were administered on days 14-28. Arthritic scores were determined, then analyzed using Kruskal Wallis followed by Mann Whitney tests. Mobility scores were analyzed using one way analysis of variance, followed by least significant difference multiple comparison test. Arthritic joint histopathology was observed on day 29.

RESULTS

The results showed that the ethanolic extract of *J. curcas* leaves at doses of 150 mg/kg, 300 mg/kg and 600 mg/kg significantly reduced arthritis scores ($p<0.05$) compared to control group (CFA). The *J. curcas* leaf extract at doses of 150 and 300 mg/kg BW decreased mobility scores. Histopathology studies showed that the *J. curcas* extract reduced edema and cartilage destruction in arthritic joints.

CONCLUSIONS

The *J. curcas* leaf extract had anti-arthritic effects by reducing arthritis scores and mobility scores. The extract should be further examined as a potential candidate for anti-arthritic therapies.

Keywords : Antiarthritic, *Jatropha curcas*, adjuvant induced arthritis, rats

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Daun Jatropha curcas memiliki aktivitas antiartitis terhadap adjuvant-induced arthritis *pada tikus*

ABSTRAK

LATAR BELAKANG

Daun Jarak Pagar (Jatropha curcas) merupakan salah satu tanaman herbal Indonesia yang telah terbukti sebagai antioksidan dan antiinflamasi. Penelitian ini bertujuan untuk menilai aktivitas antiartritis ekstrak etanol daun Jarak Pagar pada tikus dengan model adjuvant induced arthritis *(AIA).*

METODE

*Tikus wistar jantan dibagi menjadi 6 kelompok (n=8), terdiri dari kelompok normal (NaCl 0,9%), kelompok kontrol (*complete Freund's adjuvant*/CFA), natrium diklofenak dengan dosis 6,75 mg/kg BB (p.o), dan kelompok ekstrak etanol daun J. curcas dengan dosis 150 mg/kg BB (p.o), 300 mg/kg BB (p.o) dan 600 mg/kg BB (p.o). Setiap kelompok diinduksi dengan 0,2 ml CFA (1 mg/ml) pada hari ke-1 dan diberikan injeksi booster dengan 0,1 ml CFA (1 mg/ml) pada hari ke-5. Ekstrak J. curcas diberikan pada hari ke 14-28. Skor artritis diukur, kemudian dianalisis dengan uji* Kruskal Wallis *dilanjutkan uji* Mann Whitney. *Skor mobilitas diukur dan dianalisis dengan* one way analysis of variance *dilanjutkan dengan* least significant difference multiple comparison test. *Histopatologi sendi tibioarsal diamati pada hari ke-29.*

HASIL

Hasil penelitian menunjukkan bahwa ekstrak etanol daun J. curcas pada dosis 150 mg/kg, 300 mg/kg dan 600 mg/kg mampu menurunkan skor artritis secara signifikan ($p<0,05$) dibandingkan dengan kelompok kontrol. Ekstrak J.curcas dosis 150 mg/kg dan 300 mg/kg mampu menurunkan skor mobilitas. Hasil histopatologi sendi menunjukkan bahwa J.curcas mampu menghambat edema dan destruksi kartilago pada jaringan sendi.

KESIMPULAN

Ekstrak J. curcas memiliki aktivitas menurunkan artritis dan mobilitas sendi sehingga perlu diteliti lebih lanjut potensinya sebagai antiartritis.

Kata kunci : *Antiartritis, Jatropha curcas, adjuvant induced arthritis, tikus*

INTRODUCTION

Many plants have long been recognized as important sources of therapeutically effective medicines. Traditional medicine using plant extracts continues to provide health coverage for over 80% of the world's population, especially in the developing world. Recently, the use of extracts from plants for arthritis treatment has been promoted, especially after the withdrawal of Food and Drug Administration (FDA) approved anti-inflammatory drugs. One such plant that is widely used in Asia but that has not been studied in a well-controlled experimental trial to date, is the species *Jatropha curcas*.[1] *J.curcas* belongs to the family *Euphorbiaceae* and is used in Asian traditional medicine to cure various ailments. Compounds that have been isolated from *J.curcas* leaves include the flavonoids apigenin and its glycosides vitexin and isovitexin, the sterols stigmasterol, 3-D-sitosterol and its 3-D-glucoside.[2] This plant is traditionally

used in various disorders, such as ulcers, edema, rheumatism, pain, and as a mouthwash.[3]

Previous studies have reported that the plant has been shown to possess anti-inflammatory and analgesic effects that can be used as therapy in managing inflammatory conditions or as complementary therapy allowing patients to take smaller doses of conventional anti-inflammatory drugs.[4,5] Previous investigations reported that ethanolic extracts of *J.curcas* leaves at a dose of 500 mg/kg exert their anti-inflammatory activity in Wistar rats by decreasing neutrophil recruitment.[6] The leaves of *J.curcas* had antioxidant activity by inhibition of inducible nitric oxide synthase (iNOS).[7]

Arthritis is an inflammatory disorder which affects multiple joints and causes cartilage erosion. It is a lifelong progressive disease which produces significant morbidity and premature mortality. Various inflammatory mediators produce joint inflammation resulting in pain, loss of function, joint destruction and permanent deformity after a certain time if the condition is left untreated.[8,9] This disease has a world wide distribution but its pathogenesis is not clearly understood. Although there are a few antirheumatic drugs showing effectiveness on the treatment of rheumatoid arthritis, the side effects and toxicity call for new and more effective natural drugs.[10] Adjuvant-induced arthritis is a chronic crippling, musculoskeletal disorder that is the nearest approximation to human rheumatoid arthritis for which there is at present no medicine available effecting a permanent cure.[11] The modern steroidal and nonsteroidal anti-inflammatory drugs are used for the amelioration of the symptoms of the disease, but also produce severe side effects. Over the years, an increasing proportion of patients with arthritis are resorting to complementary and alternative medicine for their health needs. The aim of this study was to evaluate the effect of an ethanolic extract of *J. curcas* leaves on adjuvant-induced arthritis in rats.

METHODS

Research design

This study used a completely randomized design (CRD) of unidirectional pattern. The research was carried out in the Laboratory of Pharmaceutical Biology, Department of Pharmacy, Faculty of Medicine and Health Sciences, Jenderal Sudirman University, Purwokerto for preparation of the extract; the Laboratory of Pharmacology and Toxicology, Pharmaceutical Faculty of Gadjah Mada University for the animal experimental study; and the Laboratory of Pathology and Anatomy, Medical Faculty of Gadjah Mada University, Yogyakarta for the histopathology study. The study was conducted from Juni to October 2013.

Animals

Studies were conducted on 48 male Wistar rats weighing 110-170 g obtained from the animal house in the Faculty of Pharmacy, Gadjah Mada University. The number of rats was determined by the formula of Federer; with the anticipation of deaths (drop outs) of 30%, thus the resulting total number of rats was 48. Animals were acclimatized to experimental conditions in cages and kept under standard environmental conditions (22 ± 3°C; 12/12 h light/dark cycle). Rats were allowed to feed and water ad libitum.

Plant material

Leaves were collected from Karangwangkal, Purwokerto. Taxonomic identification of the plant was made by the Laboratory of Taxonomy, Faculty of Biology, Jenderal Soedirman University.

Preparation of extract

The simplicia were cleaned and oven-dried at the controlled temperature of 70°C, then powdered by homogenizer. The crude drug powder was macerated in 96% ethanol for 3x24 hours. The macerate was evaporated in a rotary

evaporator for ± 90 minutes in the temperature range of 70-80°C, then evaporated over a water bath to produce a thick extract, which was stored in a refrigerator until used in the study.

Induction of arthritis

Freund's adjuvant induced arthritis model was used to assess the anti-arthritic activity of the ethanolic extract of *J.curcas* in Wistar rats. Each group was induced by 0.2 mL complete Freund's adjuvant (CFA 1 mg/ml) on day 1 and a booster injection of 0.1 ml CFA (1 mg/ml) on day 5 by intradermal injection.[12]

Intervention on adjuvant-induced arhritis

Forty-eight Wistar rats were divided into six groups (n=8). They were fed a standard diet and water was given ad libitum. The animal subjects were assigned randomly into groups, consisting of: (i) normal group, injected with 0.9% NaCl, (II) negative control group, induced by CFA, (III) positive control group, given sodium diclofenac at a dose of 6.75 mg/kg, and (IV-VI) treatment groups, given ethanol extracts *J. curcas* leaves at doses of 150 mg/kg, 300 mg/kg and 600 mg/kg. The treatment extracts and sodium diclofenac were administered orally on days 14-28. On day 29, the animals were killed by cervical dislocation.

Arthritis and mobility scores

The arthritis and mobility scores are indicators of the severity of arthritis. The arthritis and mobility scores were measured on days 0, 1, 4, 8, 12, 16, 20, 24, and 28.[13] Each paw was scored on a scale of 0-4 for the degree of swelling, erythema and deformity (maximum score 16 per animal) as follows: 0 = normal, 1 = slight erythema and/or swelling of the ankle or wrist, 2 = moderate erythema and/or swelling of ankle or wrist, 3 = severe erythema and/or swelling of ankle or wrist and 4 = complete erythema and swelling of toes or fingers and ankle or wrist and inability to bend the ankle or wrist. Whole animal mobility was scored between 0 and 4 according to the following definitions: 0 = normal, 1 = slightly impaired, 2 = major impairment, 3 = does not step on paw and 4 = no movement.[13]

Histological processing and assessment of arthritis damage

The rats were killed by cervical dislocation. Knee joints were removed and fixed for 4 days in 10% formaldehyde. After that the specimens were processed for paraffin embedding and preparation of tissue sections (7 ìm thick) and were stained with hematoxylin and eosin.

Statistical analysis

The data were analyzed using SPSS software version 17.0. All variables were checked for normal distribution using the Kolmogorov-Smirnov one sample test. The arthritis scores were analyzed using Kruskal Wallis followed by Mann Whitney test (abnormal distribution). Mobility scores were analyzed using one way analysis of variance, followed by least significant difference multiple comparison test. Values of $p<0.05$ were regarded as statistically significant.

Ethical clearance

This study was accorded ethical clearance by the Commision for Research Ethics for the Medical and Sciences, Faculty of Medicine and Health Sciences, Jenderal Soedirman University.

RESULTS

Throughout the 28-day study, all arthritic rats showed persistent increases in both arthritis and mobility scores. Following the injections of CFA, the rats developed arthritis beginning from the 8th day. In arthritic controls (group II), there was an increase in arthritis scores in the rats until the 28th day (Table 1). In the 28-day study it was found that sodium diclofenac significantly decreased the arthritic condition from the 20th day after induction by Freund's adjuvant ($p<0.05$) (Table 1). The extract at a dose of 150 mg/kg significantly decreased the arthritis scores after the 20th day ($p<0.05$) and there were

Table 1. Effect of *J.curcas extracts* on mobility scores in Freund's complete adjuvant induced arthritis in rats

Groups	Arthritic score at different time after adjuvant induction (days)								
	0	1	4	8	12	16	20	24	28
Normal	0	0	0	0	0	0	0[a]	0[a]	0[a]
Arthritic control	0	0	0	2.25 ±0.25	2.50±0.19	3.25± 0.25	3.75 ±0.16[b]	3.63 ±0.18[b]	3.63 ±0.18[b]
Standard drug	0	0	0	2.13 ±0.35	2.60±0.18	2.88± 0.13	2.88 ±0.13[a]	2.63 ±0.18[a]	2.37 ±0.18[a]
J.curcas 150 mg/kgBW	0	0	0	1.50 ±0.23	2.00±0.19	2.30± 0.29	1.80± 0.16[ab]	1.80 ±0.16[a]	1.50 ±0.13[ab]
J.curcas 300 mg/kgBW	0	0	0	2.13 ±0.23	3.00±0.19	3.13± 0.23	2.75 ±0.31[a]	2.63 ±0.18[a]	2.37 ±0.18[a]
J.curcas 600 mg/kgBW	0	0	0.13 ±0.12	2.13 ±0.29	2.88±0.13	2.75± 0.16	2.5 ±0.19[a]	2.37 ±0.18[a]	2.13 ±0.23[a]

Values expressed as mean ± S.E.M of 8 rats; a = p<0.05 compared with arthritic controls (CFA-induced); b=p<0.05 compared with standard drug (sodium diclofenac)

significant differences in arthritis scores compared with sodium diclofenac on the 20th day. Rats treated with *J.curcas* extract at doses of 300 and 600 mg/ kg showed significant decreases in arthritis scores (p<0.05) from the 20th to the 28th day compared to arthritic control rats (Table 1).

In arthritic rats the mobility scores increased (60%) on the 28th day compared with the mobility scores on the 12th day (Table 2). The mobility scores on the 12th day in arthritic rats (control and treatment groups) were increased compared with normal controls (p<0.05). The *J. curcas* leaf extract at doses of 150, 300 and 600 mg/kg decreased mobility scores on the 28th day and there were significant differences with the arthritic control group (p<0.05). Sodium diclofenac significantly decreased mobility scores (p<0.05). There were no significant differences in the activity of *J. curcas* leaf extracts on mobility score at doses of 150 and 300 mg/kg compared with sodium diclofenac (Table 2).

The *J. curcas* extract decreased inflammation, edema, and cartilage destruction in arthritic joints. Figure 1 shows the histological changes in joints of control and experimental animals, as follows: Standard drug section showing joint cavity with synovial membrane lining and normal joint space in between two articular cartilages. Section of joint cavity of arthritic rats showing proliferation with granulation tissue adjacent to the damaged articular cartilage. Section of joint cavity of

Table 2. Effect of *J.curcas* extracts on mobility scores in Freund's complete adjuvant induced arthritis in rats

Groups	n	Mobility score	
		12[st] day	28[st] day
Normal control	8	0.00 ± 0.00[bc]	0.00 ± 0.00[bc]
Arthritic control	8	1.25 ± 0.16[a]	2.00 ± 0.00[ac]
Standard drug	8	1.37 ± 0.26[a]	0.87 ± 0.23[ab]
J.curcas 150 mg/kg	8	1.12 ± 0.29[a]	1.00 ± 0.00[ab]
J.curcas 300 mg/kg	8	1.62 ± 0.18[a]	1.25 ± 0.16[ab]
J.curcas 600 mg/kg	8	1.37 ± 0.18[a]	1.37 ± 0.26[abc]

Values expressed as mean ± S.E.M of 8 rats; a = p<0.05 compared with normal controls; b = p<0.05 compared with arthritic controls (CFA-induced); c = p<0.05 compared with standard drug (sodium diclofenac)

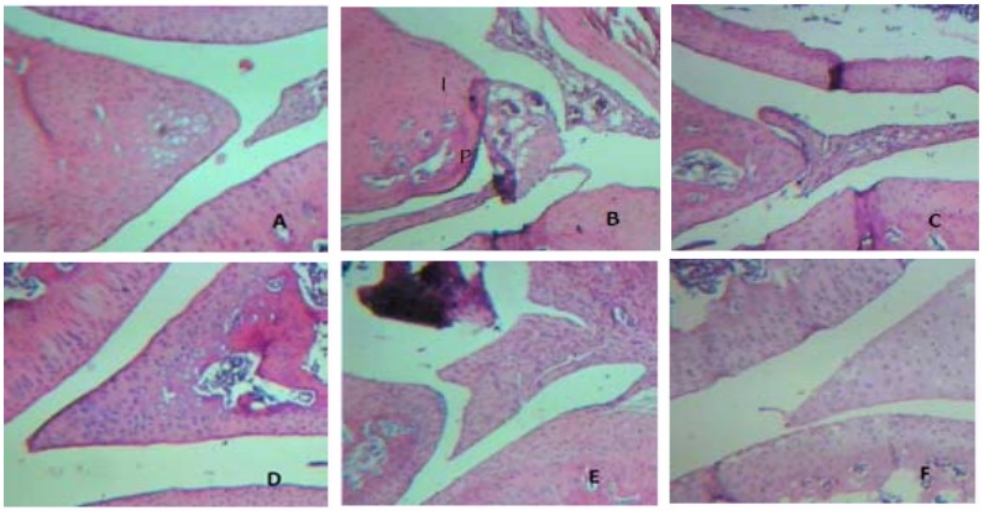

Figure 1. Histopathological representation of joints stained with H&E
(A) normal rat (B) control rat (C) diclofenac (6.75 mg/kg) treated rat (D) *J. curcas* 150 mg/kg treated rat, (E) *J. curcas* 300 mg/kg treated rat, (F) *J. curcas* 600 mg/kg treated rat. Images (X 40 magnification) are typical and representative of each study group, (I) Section of joint cavity of arthritic rats showing inflammation and (P) proliferation with granulation tissue adjacent to the damaged articular cartilage. Section of joint cavity of rats on standard drug, *J. curcas* 150 mg/kg, 300 mg/kg and 600 mg/kg showing decreasing inflammation, edema in arthritic joints and cartilage destruction

arthritic rats showing pannus. Section of joint cavity of *J. curcas* treated rats showing normal architecture of both cartilages.

DISCUSSION

This investigation on arthritic rats showed joint swellings that were noticeable around the ankle joints during the acute phase of arthritis and were due to edema of periarticular tissues such as ligaments and joint capsules. The progress of the arthritic condition was evident around day 12 which indicated systemic inflammation.[14] The joint swellings were found to be increasing in the initial phase of inflammation and becoming constant in 2 weeks (beginning on day 8). These increases in arthritis and mobility scores have been found to be associated with chronic inflamation. *J. curcas* extract at doses of 150 mg/kg, 300 mg/kg and 600 mg/kg significantly suppressed the arthritis of the paws in the chronic phase which may be due to the suppression of inflammatory mediators released as a result of induction by Freund's adjuvant.

Release of various inflammatory mediators including cytokines (IL-1B and TNF-alpha), interferons and platelet derived growth factor (PDGF) are responsible for the initiation of pain along with swelling of the limbs and joints, bone deformations and disability of joint function.[10] This is because the activation of macrophages results in the production of several cytokines including IL 1, IL 6, interferon ã (IFN ã) and TNF á which have been implicated in immune arthritis. These mediators are responsible for the pain, destruction of bone and cartilage that can lead to severe disability.[10] Pro-inflammatory cytokines such as IL-1â are potent inducers of reactive oxygen species, including nitric oxide and inflammatory mediators such as prostaglandin E2, via enhanced expression of inducible nitric oxide synthase.[15] Nitric oxide can modulate adhesion of leukocytes to the

vascular endothelium and the activity of numerous enzymes, all of which can have an impact on inflammatory process.[16]

Several studies have shown the antioxidant and anti-inflammatory properties of flavonoids. Recent studies have also shown that certain flavonoids, especially flavone derivatives, express their anti-inflammatory activity at least in part by modulation of proinflammatory gene expression such as cyclooxygenase-2, inducible nitric oxide synthase, and several pivotal cytokines.[17] Oskoueian et al.[7] found that the methanol extract of *J. curcas* at a concentration of 3.1 up to 200 ug/ml had inhibitory activity on iNOS. The leaves of *J. curcas* were strong iNOS inhibitor contributing to an anti-inflammatory effect with an IC_{50} value of 93.5 ìg/ml and NO scavenging activity of samples correlated well with the levels of phenolics, flavonoids and saponins present in the leaves.[7] Similar findings on the antiinflammatory effect of extracts from different parts of *J. curcas* plant have been reported. Mujumdar and Misar [18] observed the anti-inflammatory activity of topical application of *J. curcas* root powder paste, on 12-O-tetradecanoylphorbol-13-acetate (TPA) induced ear inflammation in albino mice. Similarly, Uche and Aprioku [19] reported the inhibitory activity of *J. curcas* leaf extract (10-80 mg/kg BB), on egg-albumin induced inflammation in Wistar albino rats. *J. curcas* extract (150 mg/kg) had anti-inflammatory effects on carrageenan-induced arthritis in rats. Saxena et al.[2] reported that the compounds which were found to be anti-arthritic are the flavonoids apigenin and its glycosides vitexin and isovitexin, the sterols stigmasterol, 3-D-sitosterol and its 3-D-glucoside.

Though the actual mechanism of suppressing the arthritic condition is not known, it can be correlated with the presence of flavonoids in suppressing the inflammation and exerting antioxidant activity.[4] Synergistic activity between polyphenolic compounds in the extract may possibly contribute to the antioxidant activity.[20] The mechanism of action of these compounds is not known. *Jatropha curcas* leaves also are antioxidants and free-radical scavengers, which may aid in suppressing reactive oxygen species (ROS) that stimulate inflammatory responses. The leaves of *J. curcas* also demonstrated potent nitric oxide and superoxide radicals scavenging (antioxidant) activity.[21] Igbinosa et al.[22] showed that phenolic compounds have the ability to absorb and neutralize free radicals, and disable oxygen species and hydroxyl radicals. From the results observed in the current investigation, it may be concluded that the *J. curcas* extract (at doses of 150 mg/kg, 300 mg/kg and 600 mg/kg) can be employed in potential anti-arthritic formulations since it was active in adjuvant-induced arthritis. A potential limitation of this study that must be considered is that only a limited number of rats were used for this study as indicated by the animal ethical clearance. It would provide better conclusions if validated with a larger sample size.

CONCLUSION

The results showed that *J. curcas* leaf had anti-arthritic activities that should be further examined as a potential candidate to be exploited for anti-arthritic therapies.

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