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Effects of the *Sonchus Arvensis* Fraction in Rats with Monosodium Urate–Induced Gouty Arthritis

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Abstract: *Sonchus arvensis* (SA) is a plant with superior health potential. Many studies have shown that this plant is useful in overcoming kidney stone disorders and has anti-inflammatory potential in synovial tissue. This study aimed to explore the anti-inflammatory potential of *Sonchus arvensis* fraction as a gouty arthritis treatment; the novelty of this study is that it proposes a new modality of gouty arthritis treatment using an SA fraction. Thirty male Wistar rats were divided into a normal control, negative control, positive control, n-hexane fraction, ethyl acetate fraction, and water fraction. Gouty arthritis was induced via injection of monosodium urate (MSU) into the intraarticular left ankle. The SA water fraction showed a more significant reduction in inflammatory cells compared with the hexane and ethyl acetate fractions. The water fraction of SA had an equal effect to the positive control in reducing inflammatory cell infiltration into the synovial tissue. In conclusion, the SA water fraction has an anti-inflammatory effect in MSU–administered rats, decreasing the infiltration of inflammatory cells into the synovial joint.

Keywords: *Sonchus arvensis*, gouty arthritis, rat.

苦苣生参成分对尿酸钠诱发痛风性关节炎大鼠的影响

摘要: 山茱萸 (萨)是一种具有卓越健康潜力的植物。许多研究表明，这种植物有助于克服肾结石疾病，并在滑膜组织中具有抗炎潜力。本研究旨在探索山竹组分作为痛风性关节炎治疗的抗炎潜力；这项研究的新颖之处在于它提出了一种使用 SA 组分治疗痛风性关节炎的新方式。30 只雄性威斯塔大鼠分为正常对照、阴性对照、阳性对照、正己烷组分、乙酸乙酯组分和水组分。痛风性关节炎是通过将尿酸单钠(密歇根州立大学) 注射到左踝关节内引起的。与己烷和乙酸乙酯部分相比，萨水部分显示出更显着的炎症细胞减少。萨的水部分在减少炎症细胞浸润到滑膜组织方面与阳性对照具有相同的效果。总之，萨水部分对密歇根州立大学给药的大鼠具有抗炎作用，减少了炎症细胞向滑膜关节的浸润。

关键词：苦荞，痛风性关节炎，大鼠。

1. Introduction

Gouty arthritis is a type of arthritis characterized by pain, synovial joint swelling, and uric acid disturbance [1]. This disorder is caused by excessive nucleic acid alteration, and it leads to monosodium urate (MSU) crystal deposition in the synovial tissue [1, 2]. MSU

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fragment accumulation in the joint synovial tissue causes an inflammatory reaction at the deposition site in the form of leukocyte infiltration, followed by phagocytosis by macrophages/monocytes. This condition results in membrane lysis, reactive oxygen species (ROS) production, and lysozyme enzyme release [2].

ROS cause oxidative stress in cells and joint tissues. Then, they stimulate the inflammatory pathway cascade because of transcription factor and nuclear factor-κB (NF-κB) activation. NF-κB activation leads to transcription and translation of the protein cytokine interleukin 1B (IL-1B) and activation of tumor necrotic factor α (TNF-α) cytokine [2, 3]. Activation of these proinflammatory cytokines leads to erosion and damage to joint tissues. Currently, the first-line therapy for gouty arthritis comprises anti-inflammatory agents (corticosteroids and nonsteroidal anti-inflammatory drugs [NSAIDs]) and colchicine [4]. However, continued use of these drugs causes uncomfortable side effects for patients. Therefore, it is desirable to explore new therapeutic modalities that are superior in dealing with inflammation caused by gouty arthritis and have minimal side effects.

Indonesia is the country with the second-largest biological wealth in the world, following only Brazil. With such enormous natural potential, it is logical that this physical wealth should be explored to acquire new therapeutic modalities for gouty arthritis. SA (field milk thistle; commonly known as *tempuyung* in Indonesia) is a plant with superior health potential [5]. Various studies have shown that this plant is useful for overcoming kidney stone disorders, and recent research has demonstrated that SA extract (SAE) can reduce inflammation in synovial tissue resulting from MSU crystal deposition [6]. The SA flavonoid content is an essential secondary metabolite that plays a role in suppressing the inflammatory process arising because of MSU crystal deposition in joint tissue via suppression of ROS activity in MSU-deposited tissue [6]. This study is the first research to explore SA extract by fractionating to optimize the specific SA content to exploit its anti-inflammatory potential in gouty arthritis.

2. Methods/Material

2.1. Preparation of *Sonchus Arvensis*

SA simplicia was collected from the Tawangmangu Herbal Research Center, Karanganyar, Indonesia. The SA extraction process was carried out by maceration, in which 500 g of simplicia was macerated with 96% ethanol for 72 h. Furthermore, a proportion was carried out between the dregs and macerate. The macerate was used for the fractionation process with n-hexane, ethyl acetate, and water solvents to obtain the n-hexane fraction (FH), ethyl acetate fraction (FE), and water fraction (FA) from SA.

2.2. Monosodium Urate Crystal Synthesis

A total of 0.8 grams of uric acid was liquefied in 155 ml of Aqua Bidest containing 5 ml of NaOH (1M), pH 7.2. The gouty blend was chilled and mixed at 22–23 °C and kept overnight at 4 °C. Next, the residue was purified from the solution, dried at 70 °C for 4 h, and prepared into powder. Then, the MSU crystal was sterilized at a temperature of 180 °C for 2 h.

2.3. Ethical Approval

Our research was conducted with approval from the Medical Research Ethics Committee, Faculty of Medicine, Universitas Sriwijaya, Palembang, Indonesia (Ref Num. 187/kptfkunsri-rsmh /2020).

2.4. Animal Model of Gout Arthritis

Thirty male Wistar rats weighing 200–250 g from Animal House Eureka in Palembang, Indonesia, were used for this study. Each rat was housed in controlled conditions under a 12 h light/dark cycle with free access to a standard laboratory diet and water *ad libitum*.

After 1 week of acclimatization, the rats were divided into six groups containing five rats each. These were labelled as the normal group (Con), MSU group (MU), MSU + colchicine (0.28 mg/kg; Pos), MSU + n-hexane fraction SA (20 mg/kg; FH), MSU + ethyl acetate fraction of SA (20 mg/kg; FE), and MSU + water fraction of SA (20 mg/kg; FA). Before MSU administration, rats in the Pos group were given colchicine (Dexa Medica, Palembang, Indonesia) at 0.28 mg/kg/day per oral for 7 days. The animals in the FH, FE, and FA groups were intubated with SA fraction once daily for 1 week. The Con and MU groups were given equal amounts of 0.9% saline solution (10 ml/kg) with sonde for a week.

On day 7, gouty arthritis was induced in the rats 1 h after treatment. The rats were anesthetized intraperitoneally with a 10% chloral hydrate injection (0.3 ml/100 g). Then, each rat in the MU, FH, FE, and FA groups was injected with MSU (50 μl) in the joint cavity of the left ankle. Each rat in the Con group received an intraarticular injection of 0.9% NaCl (50 μl) in the left ankle. Before sacrifice, the rats were anesthetized with an intraperitoneal injection of 10% chloral hydrate (0.3 ml/100 g). The intraarticular fluid was taken and centrifuged at 5,000 rpm for 10 min at a temperature of 25 °C; it was then stored at −20 °C for IL-1β testing using the enzyme-linked immunosorbent assay (ELISA) method. Meanwhile, the joint synovial tissue was evacuated, some of which were homogenized and centrifuged to obtain a supernatant in RNA later (Sigma Aldrich, Singapore) for immunoblotting tumor necrosis factor-alpha examination.

2.5. Histopathological Evaluation

The synovial tissue was fixed using alcohol and xylene with graded concentrations, paraffinized, and sliced into 4 μm thickness. The sliced tissue was put on an object glass and stained with HE. The alteration in synovial tissue was interpreted with light microscope (Olympus, Tokyo, Japan).

2.6. Enzyme-Linked Immunosorbent Assays (ELISA) for Interleukin-1 Beta

The concentration of interleukin-1 beta in intra-articular fluid was evaluated with Rat ELISA interleukin-1β (Cloud Clone, Hangzhou, China). In brief, 50 μl of standard serum samples were added to the well and placed in 37^0C for incubation for thirty minutes. Then, the plates were rinsed three times. HRP conjugates (100 μl) were put into well and incubated for another thirty minutes at 37^0C. The plates were rinsed for three times, then 50 μ of each, chromogen A and B were put into well and incubated for another fifteen minutes at 37^0C. Subsequently, 50 μ of H_2SO_4 was put into well. The plate was assessed with ELISA reader and the value obtained was 450 ηm (Biorad, California, USA).

2.7. Immunoblotting Tumour Necrosis Factor-Alpha

The ankle joint tissue was put into a RIPA buffer (Sigma Aldrich, Hangzhou, China) equipped with PMSF on frozen water for five minutes. After the centrifugation at 12000 rpm for ten minutes at 4^0C, the supernatant was obtained as protein extract. The homogenized tissue was incubated on ice for fifteen minutes and centrifuged at 5000 rpm for 5 minutes at 4^0C. Then, the supernatant was accumulated as partial cytoplasmic protein, while the pellets were extracted again in the extraction buffer. After incubation on ice for 15 minutes and centrifugation at 12,000 rpm for 5 minutes at 4^0C, the supernatant combined with the cytoplasmic proteins. The pellets were then extracted again in the extraction buffer and rattled hard for thirty minutes at 4^0C. Then, repeat the centrifugation at 13.000 rpm for ten minutes at 4^0C.

A total of 40 μg of extracted protein was taken out at 10% SDS-PAGE. Next, the isolated protein was switched to PVDF (Merck) and inhibited by fatless milk (five percent) on TBS for an hour at 22-23^0C. PVDF was stored in 4^0C (eight hours), primary antibody tumor necroting alpha (1:1000). Furthermore, the blotting results were visualized with chemiluminescence (Biorad, California, USA). Blotting was standardized by blotting β-actin.

2.8. Phytochemical Test

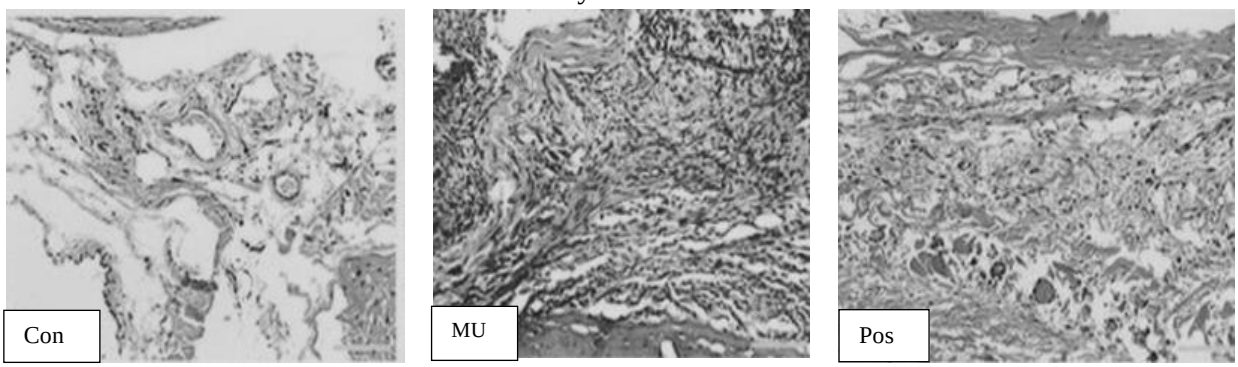
SA fraction was analyzed for phytochemical screening, including tannins, alkaloids, flavonoids, quinones, saponins, and steroids/triterpenoids. The ethyl acetate fraction was separated using TLC as a stationary phase in the form of silica gel GF254 and the mobile phase in the shape of n-hexane:chloroform:ethyl acetate (2:5:5).

2.9. Data Analysis

Values were expressed as mean ± standard deviation. A statistical analysis of the results was performed using one-way or two-way analysis of variance (ANOVA) to find differences between groups. The Bonferroni test was then used for all pair-wise comparisons. Differences were considered to be statistically significant if p-values were less than 0.05.

3. Results

In order to evaluate SA fraction efficacy on synovial joints, a tissue evacuation was performed. The MU group (negative control) presented with inflammation (Fig. 1). Additionally, the inflammation response was reduced in the SA fraction treatment group. The SA water fraction showed the most significant reduction in inflammatory cells, as compared to the hexane or ethyl acetate fractions. The SA water fraction group's effect was equal to that of the positive control in reducing inflammatory cells infiltration in the synovial tissue.



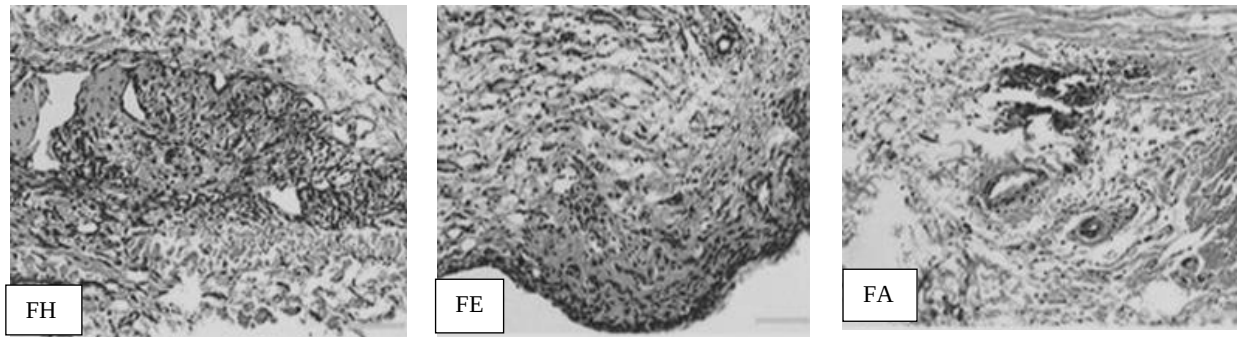


Fig. 1 Effect of fraction tempuyung on MSU-induced gout arthritis and inflammatory cell infiltration. Hematoxylin and eosin stained for histological assessment. Con - normal group, MU - MSU-induced gout arthritis, Pos - MSU-induced gout + Colchicin, FH - hexane fraction of tempuyung, FE - ethyl acetate fraction of tempuyung, FA - water fraction of tempuyung. Magnification x200

Table 1 shows that in the experimental group of animals that were injected with a monosodium-urate elevated interleukin 1 beta concentration of synovial tissue, the monosodium-urate injection caused an inflammation of the synovial tissue. The administration of an SA fraction showed its ability to reduce the IL-1B levels with the largest decrease being in the group that received the SA water fraction treatment.

Table 1 Level of IL-1β in synovial fluid

No.	Group	IL-1β (pg/mL) ± SD	P-Value*
1.	Con	28,26 ± 3,41	0,00
2.	MU	496,23 ± 15,43	-
3.	Pos	97,41 ± 7,21	0,00
4.	FH	386,12 ± 21,43	0,00
5.	FE	298,11 ± 18,65	0,00
6.	FA	155,83 ± 10,12	0,00

* VS MU; ANOVA, pos hoc Bonferroni; p < 0,05

Fig. 2 shows the potential of the SA fraction to reduce pro-inflammatory cytokine protein expression (i.e., tumor necroting factor-α). Furthermore, SA water fraction lowered the tumor necroting factor-α expression more effectively than the hexane and ethyl acetate fractions.

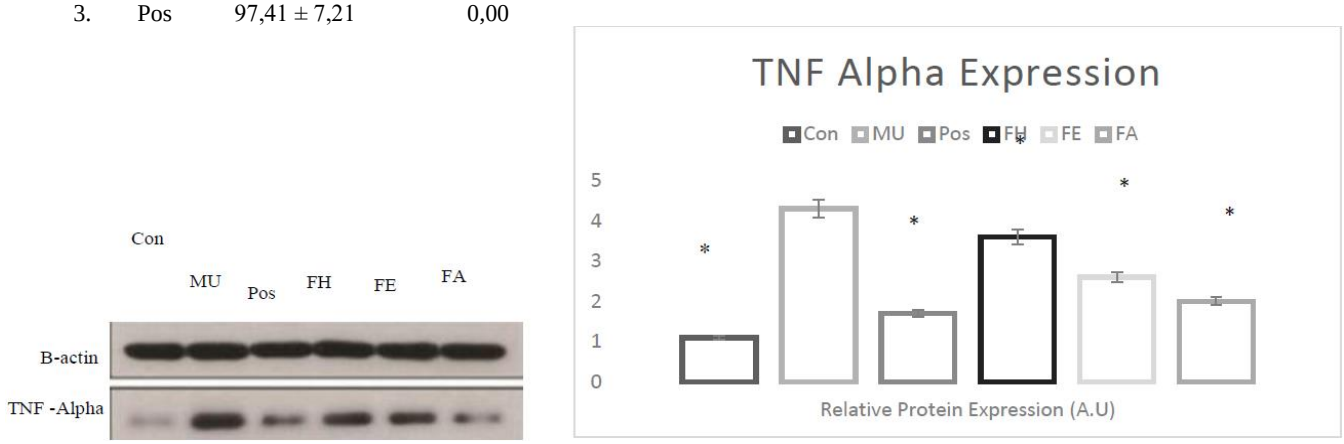


Fig. 2 Effect of tempuyung faction on MSU-induced TNF alpha activation in synovial of rats
* P < 0,05 VS model group; ANOVA, pos hoc Bonferroni

Table 2 shows that each segment exhibits a difference in the content of the active metabolites contained. The segment is rich in triterpenoids and steroids, while the water segment is rich in flavonoids.

Table 2 Phytochemical test of tempuyung fraction

Test material	Saponin	Alkaloid	Triterpenoid	Steroid	Flavonoid
FH	+	-	++	++	-
FE	+	+	-	+	+
FA	+	+	+	+	++

4. Discussion

As the quality of life improves, incidences of gouty arthritis increase. Gouty arthritis is a joint disorder that is caused by inflammation due to monosodium urate fragments that accumulate in the joints. The mechanism of gouty arthritis has been studied for years and is an inflammatory cascade activation that is induced by monosodium urate fragments [7]. Nuclear factor-kappa beta (nuclear factor-κB) initiates pro-inflammatory cytokine gene expression, which causes an inflammatory response in gouty arthritis.

In contrast, tumor necroting factor-alpha (TNF-α) and interleukin-1 beta (IL-1β) overexpression can stimulate the nuclear factor-κB pathway and cause inflammation and articular damage [8]. Monosodium urate fragments inhibit the nuclear factor-κB production, move the nuclear factor-κB to the nucleus,

and control different target genes transcription [8, 9]. In our study, the IL-1β and TNF-α serum levels were considerably elevated in response to monosodium urate fragments.

The exploration of herbal plants is important to reduce the severity of gouty arthritis, alongside therapy with minimal side effects [10]. The herb *Sonchus arvensis* (*S. arvensis*) has the optimal potency for the management of gout arthritis [5, 6]. This study showed that *S. arvensis* can decrease inflammation in ankle joints. Our study indicated that *S. arvensis* extract can lower the inflammatory mediator and the expression of IL-1β and TNF-α. Neutrophil, which accumulates in the synovial fluid, is the main characteristic of gout arthritis [7]. After the monocytes and neutrophils have been activated, these cells will phagocytose monosodium urate fragments, which further encourages an inflammatory response from caspase [11, 12]. Hence, preventing inflammatory cell infiltration may be a strong therapeutic strategy in gout arthritis [13]. The histopathological results in this research showed that the water fraction of the *S. arvensis* dosage significantly attenuated inflammatory cells' infiltration into the synovium due to monosodium urate fragments and synovial hyperplasia. The water fraction shows that it is rich in secondary metabolites and flavonoids, where flavonoids are compounds that act as antioxidants. The antioxidant ability of flavonoids suppresses oxidant activity (reactive oxygen species) [6, 10]. Suppressing reactive oxygen species' activity will decrease the action of the inflammatory cascade in synovial tissue.

5. Conclusion

Our study shows that the water fraction of *S. arvensis* significantly decreases the inflammatory response in the synovial joint in gouty arthritis-induced rats. The exploration of the *S. arvensis* fraction aimed to find a new modality in gouty arthritis treatment. The decrease in the inflammatory response after *S. arvensis* fraction treatment provides hope for treating gouty arthritis. The decreased levels of IL-1β and TNF-α in synovial joints showed that the *S. arvensis* fraction was effective at reducing inflammation. The fractionation process when extracting S. arvenis allows flavonoids and other active substances to reduce the inflammatory response in gouty arthritis. However, one limitation of this research is that it was conducted using animal models (*in vivo*), which means that its application in clinical practice requires further research.

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