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Research Article

Anti-Inflammatory Potential of *Brucea javanica* Fruit

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Abstract

Objective: Inflammation plays a crucial role in the progression of many diseases, excessive inflammation increases immune cell activation, which can destroy tissues and body health. When inflammation occurs, multiple pro-inflammatory mediators are overproduced, leading to a variety of diseases such as rheumatism, diabetes, and cardiovascular problems. *Brucea javanica* has been used as traditional medicine as a therapy for anti-tumor, amebic dysentery, diarrhea, malaria, and intestinal inflammation. Therefore, in this study, we explored the effect of ethanol extract *Brucea javanica* Fruit on anti-inflammation activity in carrageenan-induced rat paw edema and the COX-2 inhibitory effect in vivo.

Methods: In vivo anti-inflammatory activity of the ethanolic extracts was evaluated using the carrageenan-induced rat paws edema method at doses of 50, 100, and 200mg/kg and further investigated the effect of Cyclooxygenase-2 inhibitory using ELISA readers.

Results: The ethanolic extract of *Brucea javanica* Fruit exhibited anti-inflammatory activity by oral intake of 50 mg/kg of the ethanolic extract and *Brucea javanica* inhibited rat paw edema by 50.91% significantly compared to Celecoxib by 58.52%. Moreover, *Brucea javanica* showed COX-2 inhibition by 16,40% compared to Celecoxib by 20,50%.

Conclusions: These findings indicate that *Brucae javanica* Fruit extracts have promising anti-inflammatory activity directed against COX-2 enzymatic activity.

Keywords: Anti-inflammatory, *Brucea javanica*, Malur, Buah Makasar, Cyclooxygenase.

INTRODUCTION

Inflammation plays a crucial role in the progression of many diseases, excessive inflammation augments the activation of immune cells, which can destroy the tissues and body health [1]. Multiple pro-inflammatory mediators are over-produced when inflammation occurs and leads to a series of diseases, such as rheumatism, diabetes, and cardiovascular ailments[2,3].

Anti-inflammatory drugs such as Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) are the most successful drugs used in the world by a large number of patients [4]. However, NSAIDs can cause various side effects including gastrointestinal (GI), and cardiovascular (CV) disturbances, high blood pressure, kidney toxicity, worsening of congestive heart failure, and hepatotoxicity [5–7].

Plants have played an important role in maintaining human health and improving the quality of human life for hundreds of years and serve as highly valuable medicines [8–11]. Natural medicines have been increasingly used in recent years as alternative treatments for inflammation due to their relatively mild side effects [12–16]. Previous studies have found that various plants have different pharmacological activities, including anti-inflammatory activity [17–19]. One of the plants known to have many benefits, including Malur (*Brucea javanica*).

Brucea javanica has been shown to have activities such as antitumor [20], antidiabetic[21], antihyperlipidemic[22], antioxidant, and antibacterial [23].

Thus, In this study, we investigated the effect of ethanol extract *Brucea javanica* Fruit on anti-inflammation activity in carrageenan-induced rat paw edema and the COX-2 inhibitory effect in vivo.

MATERIALS AND METHOD

Materials

Rat PTGS2/COX-2 (Prostaglandin G/H synthase 2) ELISA Kit was purchased from Fine Biotech Co., Ltd. (Wuhan, China). Celecoxib was purchased from Pfizer Inc. (New York, NY, US). Carrageenan was obtained from Sigma-Aldrich (St. Louis, MO, USA) and other reagents were purchased from Bratachem (Indonesia).

The *Brucea javanica* Fruit were collected from Surantih, West Sumatera, Indonesia. The *Brucea javanica* were identified by Dr. Nurainas, a botanist at Herbarium of Andalas University, West Sumatera, Indonesia.

Preparation of The Ethanol Extract of *Brucea javanica* Fruit (EEBjF)

The *Brucea javanica* Fruit was sun-dried. The dried *Brucea javanica* was powdered using a conventional grinder. The powdered materials were then soaked in Ethanol (70%) for 24

hours by stirring at room temperature. The materials were filtered after 24 hours. The procedure was repeated three times. The filtrates were mixed and concentrated under vacuum using a rotary until a brownish semisolid extract was obtained, free of solvent. The extract was kept cold for further pharmacological testing.

Experimental Animal

18 adult male Wistar rats with body weights of 200–250 g and aged 2-3 months were obtained from West Sumatera animal houses were used for this study. Animals were housed and cared for in standard conditions with 12 h light/dark circle and were fed with a standard pellet diet and water ad libitum. All the animals were acclimatized for a minimum period of 1 week prior to the experiment. After 1 week, animals were randomly selected for different experimental groups (3 animal/ group) and used for the in vivo determination of anti-inflammatory activity. The rats were deprived of food, but not water, for 18–20 hours before an experiment.

Phytochemical Screening

The qualitative phytochemical screening of the extracts was performed to identify the main groups of chemical constituents (alkaloids, saponins, steroid, terpenoids, flavonoids, and phenols) present in the extracts using color reactions [24].

Evaluation of Anti-Inflammatory activity

The anti-inflammatory activity was further examined by the carrageenan-induced rat paw edema method according to the method of Winter et al [25]. The experimental groups consisted of 18 rats split into six groups, Group I: Negative control (Na.CMC 0,5% p.o only), Group II: positive control (Carrageenan 1% s.c), Group III: Carrageenan 1% s.c + EEBjF (50 mg/kg BW p.o), Group IV: Carrageenan 1% s.c + EEBjF (100 mg/kg BW p.o), Group V: Carrageenan 1% s.c + EEBjF (200 mg/kg BW p.o), Group VI: comparative group (Carrageenan 1% s.c + Celecoxib 9 mg/kg p.o) were given 1 h before the injection of carrageenan.

By injecting 0.1 ml of 1% carrageenan in 0.9% saline into the right hind paw of the rat, edema was caused. After 1 h, 0.1 ml 1% carrageenan was injected subcutaneously into the subplantar area of the right hind paw of each rat except those in Group I. Edema volume was determined every 1 hour for up to 6 hours after carrageenan administration. The paw volumes were measured by a plethysmometer. The volume difference between before and after the right paw injection was measured to obtain the results. The inflammation degree of the paw and the rate of edema inhibition were calculated as follows:

% edema inhibition = (Vc −Vt) × 100/ Vc;

Vc and Vt are the average edema volumes of the control and test groups, respectively. The animal blood was collected in a heparin-coated tube at the end of the third hour. Groups I–VI was used to determine the activities of COX-2.

Evaluation of COX – 2 Inhibitory Activity Rat serum was prepared at the 3rd hour after induction of Carrageenan 1%. EEBjF (50, 100, and 200 mg/kg BW) was used for inhibition studies.The ability of the test compound to inhibit COX-2 was determined by using the Enzyme-Linked Immunosorbent Assay (ELISA) kit according to the manufacturer's instructions. The product of this enzymatic reaction produced a distinct yellow color, determined by spectrophotometrically (Microplate reader) at 450 nm.

Statistical Analysis

The statistical software SPSS version 25 (SPSS Inc., Chicago, IL, USA) was used to analyze the data. Data were analyzed using one-way ANOVA followed by Duncan's multiple range test. $p < 0.05$ was considered significant.

RESULT AND DISCUSSION

Phytochemical Screening

The qualitative phytochemical screening of EEBjF revealed that alkaloids, terpenoids, steroids, flavonoids, saponins, and phenol were present in EEBjF, as shown in table 1.

Table 1. Phytochemistry screening test result of *Brucea javanica*

	Groups	Result
I	Alkaloid	+
II	Falvonoid	+
III	Phenolic	+
IV	Saponin	+
V	Steroid	+
VI	Terponoid	+

Anti-inflammatory Activity

In the present study, the edema was measured for 6h after carrageenan injection. EEBjF given at dose 50, 100, and 200 mg/kg BW were effective in inhibiting the induced paw edema (Table 2).

Tabel 2. Anti-inflammatory activity of *Brucea javanica* extract

	Groups	Dose (mg/kg B.W)	Percentage (%) of paw edema inhibition[a]
I	Negative control (Na. CMC 0,5%)	-	
II	Positive control (0,1 mL Carrageenan **1%**)	-	-
III	EEBjF	50	**50,91***
IV	EEBjF	100	**36,96***
V	EEBjF	200	**8,37**
VI	Celecoxib[b]	9	**58,52***

[a]Data are expressed as the mean of Three observations (n = 3), bUsed as comparative group

* Significant difference compared to the positive control ($P < 0.05$)

Table 2 shows the effect of EEBjF and standard drug as compared to carrageenan control at different hours in the carrageenan-induced paw edema model. From Table 2, a significant anti-inflammatory activity of EEBjF could be confirmed through paw edema inhibition by 50,91%, 36,96% and 8,37% after 6 h, at 50, 100, and 200 mg/kg dosage, respectively, while celecoxib diminished paw edema by 58,52% at the same time. These results demonstrate that the EEBjF (50, 100, and 200 mg/kg) significantly inhibited the inflammatory processes induced by the injection of

carrageenan (p<0,005). These findings indicate that the EEBjF posses potent anti-inflammatory properties.

COX-2 Inhibitory Effect

The COX-2 Inhibitory effect of EEBjF could be confirmed through COX-2 inhibition by 16,40 %, 7,90 % and 3,80% after 3 h, at 50, 100, and 200 mg/kg dosage, respectively, while celecoxib diminished paw edema by 20,50 % at the same time. These findings show that the EEBjF (50, 100, and 200 mg/kg BW) significantly inhibited COX-2 (p<0,005). However, EEBjF (50 mg/kg BW) was the most potent COX 2 Inhibitory effect dose (Table 3).

Figure 1. clearly shows that a dose of 50mg/kg BW showed the most potency in inhibiting inflammation and inhibiting the enzyme cyclooxygenase-2.

Table 3. Cyclooxigenase-2 inhibitor Activity of *Brucea javanica* extract

	Groups	Dose (mg/kg B.W)	**Percentage (%) of Cox-2 inhibition[a]**
I	Negative control (Na. CMC 0,5%)	-	-
II	Positive control (0,1 mL Carrageenan **1%**)	-	-
III	EEBjF	50	**16,40**
IV	EEBjF	100	**7,90**
V	EEBjF	200	**3,80**
VI	Celecoxib[b]	9	**20,50**

aData are expressed as the mean of Three observations (n = 3), bUsed as comparative group

* Significant difference compared to the positive control (P < 0.05)

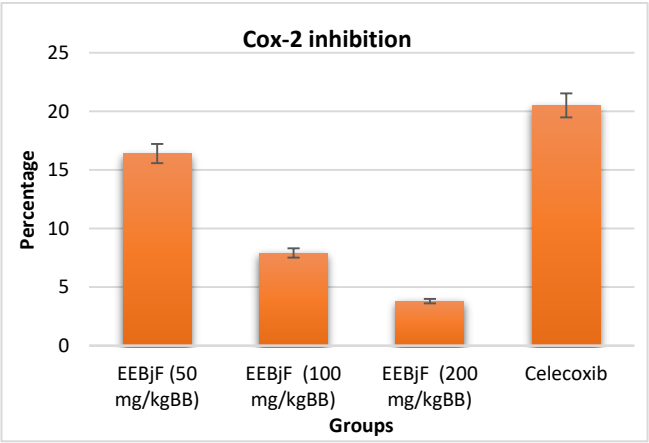

Figure 1. Comparison of percent inhibition of inflammation and percent inhibition of cyclooxygenase-2 enzyme at 3 hours after carrageenan induction.

DISCUSSION

Carrageenan-induced paw edema is a useful phlogistic tool for studying systemic anti-inflammatory drugs. This two-phase test is sensitive to the majority of clinically effective anti-inflammatory drugs. The first phase, which occurs within 1-2 hours of carrageenan injection, is caused by the release of serotonin as well as an increase in bradykinin, histamine, and prostaglandins in the inflammatory location. The second phase occurs 3-5 hours after carrageenan injection and is associated with kinin and prostaglandin production and release in the inflamed area [26,27]. Throughout the second phase, The macrophages are known to produce more interleukin-1 (IL-1) which caused an increase in the accumulation of polymorphic nuclear cells (PMNs) in the inflammatory area. The lysosomal enzymes and active oxygen species released by activated PMNs cause connective tissue destruction and paw swelling [28].

This study reported the anti-inflammatory activity of the ethanolic extract of *Brucea javanica* Fruit and the possible anti-inflammatory mechanism in the experimental model. In the present study, the EEBjF (50, 100, and 200 mg/kg) significantly inhibited the inflammatory processes. This is indicated by the ability of EEBjF to significantly decrease rat paw swelling as shown in Tables 2. The study concluded that a dose of 50mg/kg EEBjF showed the highest percent inhibition of inflammation.

These results further corroborate previous studies that the Ethyl acetate fraction and Methanol extract of *Brucea javanica* seed at the dose of 50 mg/kg significantly reduced blood glucose levels [29,30]. Other studies reported that *Brucea javanica* fruit seed extract exhibited the optimumanti-inflammatory activity at a concentration of 1%, with a 55.47%inhibition of protein denaturation[31]. Moreover, the leaves extract of *Brucea javanica* showed anti-inflammatory activity[32].

COX and 5-LOX are two key enzymes involved in the production of inflammatory mediators. Cox inhibitors are the main deviations from current pain, inflammation, and fever control therapy [33]. Many COX-2 or 5-LOX inhibitors have been developed as anti-inflammatory drugs, but some have been withdrawn from the market, indicating the need for inhibitors with few side effects [34]. Nonsteroidal anti-inflammatory drugs (NSAIDs) exert their analgesic effects by inhibiting cyclooxygenase activity, antipyretic, anti-inflammatory, and antithrombotic effects [35,36]. The anti-inflammatory potential of *Brucea javanica* Fruit may be due to the presence of active phytoconstituents such as flavonoids [37]. The previous report describes flavonoids can reduce the risk of atherosclerosis and atherothrombotic disease and several other inflammatory diseases [38–40]. The flavanol quercetin was found to suppress the expression of COX 2 mRNA in rat paw pouch exudates cells, indicating that quercetin's anti-inflammatory action may be due in part to suppressing COX-2 up-regulation[41]. Because of their powerful antioxidant capacity, flavonoids can interfere with the oxidative synthesis of (Arachidonic Acid) AA from phospholipids and reduce the downstream production of inflammatory metabolites from AA metabolism, oxidative damage, and the initiation of inducible pathways of inflammation[42]. Other studies have demonstrated that flavonoids with antioxidant properties can reduce the cellular conversion of AA to MDA (Malondialdehyde) in patients with chronic inflammation[43]. Radical scavenging activities of phenolic and polyphenolic compounds have been shown in previous studies [44,45]. There are also many studies on anti-inflammatory activities of plant extracts that contain flavonoids [46]. Furthermore, *Brucea javanica* Fruit possessed enormous potential as a medicinal drug, particularly in cancer treatment and antioxidant [23]. The significant antioxidant capacity and flavonoid content of the extract used may have contributed to the anti-inflammatory effect [47,48].

This is the first report on the potent COX-2 inhibitory properties of ethanol extract of *Brucea javanica* Fruit. The obtained results suggest that the biological effects of this natural compound may be due to inhibition of prostaglandin synthesis via the arachidonic acid pathway.

CONCLUSIONS

From the results of the present investigation, it can be concluded that the ethanol extract of *Brucea javanica* Fruit (EEBjF) possesses significant anti-inflammatory activity. The mechanism of anti-inflammatory action is thought to be mediated by COX-2 inhibition. The results presented also suggest the need for further research on the COX-1 inhibitory effect.

CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest.

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