Original Article

Evaluation of antioxidant and antipyretic effects of ethanolic extract of Cep-cepan leaves (*Castanopsis costata* (Blume) A.DC)

Maulana Yusuf Alkandahri[1]*, Maya Arfania[1], Ermi Abriyani[1], Dadan Ridwanuloh[1], Farhamzah[1], Lia Fikayuniar[1], Dadang Muhammad Hasyim[2], Nurul[2], Diah Wardani[2]

[1]Faculty of Pharmacy, University of Buana Perjuangan Karawang, Karawang, West Java, Indonesia. [2]Diploma Program of Pharmacy, Karsa Husada Garut College of Health Sciences, Garut, West Java, Indonesia.

Correspondence: Maulana Yusuf Alkandahri, Faculty of Pharmacy, University of Buana Perjuangan Karawang, Karawang, West Java, Indonesia. alkandahri@gmail.com

ABSTRACT

Almost all current antipyretic drugs irreversibly inhibit COX-2 with high selectivity; hence, they are toxic to liver cells, glomeruli, brain cortex, and heart muscle. Meanwhile, natural COX-2 inhibitors have been widely reported to have relatively few side effects. The leaves of Cep-cepan (*Castanopsis costata*) are often used to treat fever, but no studies have confirmed this effect. This study aims to determine the antioxidant effects in the DPPH model, the antipyretic activity of EECC in peptone-induced fever rats, and the acute toxicity study. EECC was obtained by the maceration method using 70% ethanol as solvent, then it was tested for its antioxidant activity. The antipyretic activity was tested using peptone-induced fever rats. The male rats used were divided into six groups for each test. The individual group consisted of 4 rats, namely, negative and positive control treated with paracetamol 150 mg/kg, as well as EECC doses of 25, 50, 100, and 200 mg/kg. An acute toxicity study was conducted at a single oral dose of 500, 1000, 2000, and 5000 mg/kg for 14 days. EECC showed a maximum antioxidant activity of 91.95% at a concentration of 200 µg/mL with an IC_{50} value of 49.28 µg/ml. Meanwhile, the maximum antipyretic effect observed at a dose of 200 mg/kg was 90.50%. The response observed in paracetamol was 97.29%. No mortality or any significant signs of toxicity was recorded for acute toxicity. Based on the results, EECC has an antioxidant effect in DPPH as well as an antipyretic in a peptone-induced mouse model.

Keywords: *Castanopsis costata*, Antioxidant, Antipyretic, Acute toxicity, Pepton

Introduction

Pyrexia or fever is a common clinical sign characterized by increased body temperature beyond normal limits. This condition causes the body to create a suitable environment for natural defense mechanisms, thereby facilitating the repair of damaged tissue or rendering infectious agents unable to survive. Infected or damaged tissue produces different inflammatory mediators, which increase the synthesis of prostaglandin E2 in the hypothalamus, causing a rise in body temperature [1]. Furthermore, fever is usually accompanied by discomforts such as pain (myalgia), lethargy, anorexia, inability to concentrate, increased muscle tone, and chills [2]. PGE2 is produced by the enzyme cyclooxygenase-2, which is inhibited by nearly all current antipyretic medications (COX-2). Because it persistently and specifically inhibits COX-2, this synthetic medication is harmful to liver cells, glomeruli, cerebral cortex, and the heart's muscular fibers [3]. On the other hand, natural COX-2 inhibitors have a lower risk of adverse effects [4]. This implies that natural antipyretic agents will induce minimal or no toxicity.

Ethnic cultures worldwide have traditionally employed medicinal plants or their formulations to prevent and/or treat several chronic ailments. For the most part, people throughout the world still rely on traditional medical systems for their health care, despite the latest technical improvements and medical advances [5]. Currently, many drugs are being developed from plants, active against various diseases. Most involve isolating

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active ingredients, namely chemical compounds found in certain medicinal plants and subsequently modified [6, 7]. Indonesia has the second-largest forest biodiversity in the world, with 28,000 plant species, of which 2,500 species, including *Castanopsis costata*, commonly known as "Cep-cepan," are used medicinally [8]. *C. costata* is known to have therapeutic activity as an antipyretic, relieve digestive problems, analgesic, and antidiabetic [9, 10]. Traditionally, this plant is often used to treat fever, but no studies have confirmed this effect. Therefore, this study aims to evaluate the antioxidant effects, antipyretic effects, and acute toxicity of the ethanolic extract of *C. costata* (EECC).

Materials and Methods

Preparation of plant and determination

Fresh leaves of *C. costata* were obtained from the traditional market of Pancur Batu, North Sumatra, Indonesia. It was legalized as a plant by botanists from the Department of Biology, Faculty of Mathematics and Natural Science, Universitas Padjadjaran (Code: 219/HB/04/2017). Next, about 10 kg of fresh leaves were transported to the Pharmacognosy Laboratory, Universitas Buana Perjuangan Karawang, for extraction.

Extraction

A total of 1.5 kg leaves powder was macerated in 70% ethanol for 3x24 h to obtain a liquid extract. It was then concentrated using a rotary evaporator at 40-50°C to a concentration of approximately 35.50%, namely the fixed weight of the extract divided by the weight of the simplicia multiplied by 100 percent.

Determination of antioxidant activity

According to Kusumawati *et al*. [11], the antioxidant activity was measured using the DPPH method. Methanol dissolved 5 mg of DPPH, giving us a stock solution of 50 g/ml. Dissolving 250 mg of EECC in 25 ml of methanol and diluting it to 25, 50, 100, and 200 g/ml yielded the sample solution. Two milliliters of each solution were combined with two milliliters of DPPH and incubated for 30 minutes at 30°C until homogenous. At a wavelength of 515.50 nm, the antioxidant activity was measured using UV-Vis spectrophotometry (Thermo Fisher Scientific, USA) four times. One milliliter of the solution in the blank sample was tested at the same time and wavelength as the DPPH solution (Ab). The ascorbic acid concentrations tested were 25, 50, 100, and 200 g/ml, which was utilized as a standard for comparison. This equation was used to determine the proportion of DPPH radical scavenging activity.

$$Inhibition\ rate\ (\%) = \frac{Ab - As}{Ab} \times 100 \quad (1)$$

The absorption of blanks and samples is shown by Ab and As, while the percentage inhibition was plotted versus concentration and determined from the IC_{50} graph.

Acute toxicity study

Acute oral toxicity has been assessed according to the OECD-425 guidelines [12]. Four groups consisted of ten rats (male and female). Each individual was given p.o doses of 500, 1000, 2000, and 5000 mg/kg of EECC. Meanwhile, rats from the control group were treated with vehicle only (1% PGA). The groups have been monitored for 14 days. The rats weighed every day, and any changes in their behavior and any symptoms of distress were carefully recorded.

Antipyretic activity

Wistar strain male rats weighing 150-200 grams were divided into six groups consisting of four in each. The individual group was given 1% PGA orally, paracetamol 150 mg/kg, and EECC at various doses of 25, 50, 100, and 200 mg/kg as a negative and positive control as the test group, respectively. Initial rectal temperature was recorded using a thermometer to a depth of 1.5 cm in the rodent's rectum. Furthermore, the induction of fever was confirmed by a temperature increase of more than 0.5 °C. In comparison, test animals that showed a temperature rise of less than 0.5 °C were excluded from the experiment [13]. Each of the test animals received 0.5 mL of aqua pro injection with 5% peptone solution. Rectal temperatures were measured again at 1, 2, 3, and 4 hours after the medication delivery. The following calculation was used to determine the percentage decrease in fever.

$$\text{Percent reduction} = \frac{B - Cn}{B - A} \times 100 \quad (2)$$

Description:

1. **B** is the temperature after pyrexia induction;
2. **Cn** represents after 1, 2, 3, and 4 hours;
3. **A** is the normal body temperature.

Statistical analysis

Data were analyzed using SPSS version 22; for statistical analysis, a one-way analysis of variance was used and followed by the Tukey HSD post-hoc test. The results are presented as mean±SEM with $p<0.05$ considered significant.

Results and Discussion

Antioxidant activity

The IC_{50}, or inhibitory concentration necessary to block 50% DPPH free radicals, was used to quantify antioxidant activity using the DPPH technique. Several concentrations ranging from 25 to 200 µg/mL EECC were tested for antioxidant activity in the DPPH model. EECC showed a maximum antioxidant activity of 91.95% at 200 µg/mL **(Figure 1)** with an IC_{50} value of 49.28 µg/mL.

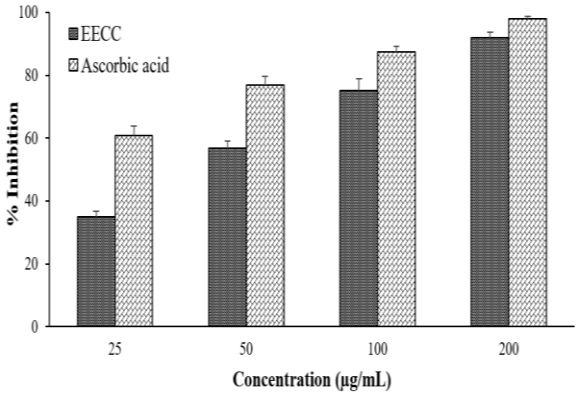

Figure 1. In vitro DPPH scavenging activities of EECC. Four replicates in each group are used to calculate the mean±SEM, with $p<0.05$ considered significant.

Tested samples showed a significant increase in antioxidant activity with increasing dosages. The DPPH technique employed ascorbic acid as a reference medication to measure antioxidant activity. At 200 µg/mL, the inhibition percentage was 98.05%, while the IC_{50} value was 20.88 µg/mL, as shown in **Table 1**.

Table 1. IC_{50} Value of EECC compared with ascorbic acid.

Samples	DPPH• IC_{50} (µg/mL)	Antioxidant activity [14]
EECC	49.28 ± 1.12	Very strong
Ascorbic Acid	20.88 ± 1.58	Very strong

This study's findings were summarized as the mean±SEM for all four replicates with $p<0.05$ considered significant. Meanwhile, In order to determine the IC_{50} value at 50% inhibition, we used the AAT Bioquest tool to analyze the regression graph.

Acute oral toxicity

A dosage range of 500-5000 mg/kg for all test samples did not produce any mortality or unusual signs of toxicity or behavioral deviations during the acute oral toxicity test. The outcomes revealed that the research samples introduced in this study did not have toxic impacts on animal models up to 5000 mg/kg. The toxicity indices for agility, tremor, convulsion, breathing pattern, lethargy, and coma exhibited by the animal groups are shown in **Table 2**.

Table 2. The toxicity index was shown by various treatment groups.

Treatment groups	Toxicity index ((+) mild, (++) moderate, (+++) severe, (×) nil)					
	Agility (1)	Tremor (2)	Convulsion (3)	Breathing pattern (4)	Lethargy (5)	Coma (6)
Control (1% PGA)	**1**	**2**	**3**	**4**	**5**	**6**
1st animal	++	×	×	×	×	×
2nd animal	++	×	×	×	×	×
3rd animal	++	×	×	×	×	×
4th animal	++	×	×	×	×	×
5th animal	++	×	×	×	×	×
6th animal	++	×	×	×	×	×
7th animal	++	×	×	×	×	×
8th animal	+++	×	×	×	×	×
9th animal	++	×	×	×	×	×
10th animal	++	×	×	×	×	×
EECC 500 mg/kg	**1**	**2**	**3**	**4**	**5**	**6**
1st animal	++	×	×	×	×	×
2nd animal	++	×	×	×	×	×
3rd animal	++	×	×	×	×	×
4th animal	+	×	×	×	×	×
5th animal	++	×	×	×	×	×
6th animal	++	×	×	×	×	×
7th animal	++	×	×	×	×	×
8th animal	+	×	×	×	×	×
9th animal	++	×	×	×	×	×
10th animal	++	×	×	×	×	×
EECC 1000 mg/kg	**1**	**2**	**3**	**4**	**5**	**6**
1st animal	+	×	×	×	×	×
2nd animal	+	×	×	×	×	×
3rd animal	++	×	×	×	×	×
4th animal	++	×	×	×	×	×
5th animal	+++	×	×	×	×	×
6th animal	++	×	×	×	×	×
7th animal	+++	×	×	×	×	×
8th animal	++	×	×	×	×	×
9th animal	++	×	×	×	×	×
10th animal	++	×	×	×	×	×
EECC 2000 mg/kg	**1**	**2**	**3**	**4**	**5**	**6**
1st animal	+++	×	×	×	×	×
2nd animal	++	×	×	×	×	×
3rd animal	+++	×	×	×	×	×
4th animal	++	×	×	×	×	×
5th animal	++	×	×	×	×	×
6th animal	++	×	×	×	×	×
7th animal	+	×	×	×	×	×
8th animal	++	×	×	×	×	×
9th animal	++	×	×	×	×	×
10th animal	+++	×	×	×	×	×
EECC 5000 mg/kg	**1**	**2**	**3**	**4**	**5**	**6**
1st animal	++	×	×	×	×	×
2nd animal	++	×	×	×	×	×
3rd animal	++	×	×	×	×	×
4th animal	++	×	×	×	×	×
5th animal	++	×	×	×	×	×
6th animal	++	×	×	×	×	×
7th animal	++	×	×	×	×	×
8th animal	++	×	×	×	×	×
9th animal	+++	×	×	×	×	×
10th animal	++	×	×	×	×	×

Antipyretic activity

The antipyretic activity of the EECC was determined by inducing fever in experimental animals and then administering various doses of EECC orally compared with the negative control. Rectal temperature was recorded immediately at 0 hours, then continued at 1, 2, 3, and 4 hours. The results showed that EECC

at 200 mg/kg significantly decreased the rectal temperature ($p<0.05$), as shown in **Table 3**. The maximum antipyretic effect observed at a dose of 200 mg/kg was 90.50% ($p<0.05$), while those of 25, 50, and 100 mg/kg was 59.34%, 54.82%, and 71.87% respectively. Meanwhile, the estimated value of Paracetamol was 97.29% ($p<0.05$). The percent inhibition of fever is shown in **Figure 2**.

Table 3. Effect of EECC in peptone-induced pyrexia in rats.

Treatment groups	Dose (mg/kg)	The of Rectal Temperature (°C)					
		Normal	0 h	1 h	2 h	3 h	4 h
NC	1% PGA	36.68±0.11	38.15±0.16	37.95±0.12	37.97±0.27	37.82±0.33	37.70±0.31
PC	150	36.30±0.10	38.00±0.16	37.60±0.10	36.80±0.18**	36.57±0.13**	36.37±0.10**
EECC	25	36.66±0.11	38.07±0.16	37.73±0.45	37.58±0.51	37.33±0.30	37.20±0.25
	50	36.40±0.10	37.98±0.11	37.78±0.38	37.33±0.39	37.18±0.33	37.08±0.26
	100	36.70±0.50	38.03±0.11	37.95±0.25	37.80±0.34	37.38±0.35	36.98±0.33
	200	36.67±0.11	38.00±0.10	37.50±0.12	37.10±0.15	36.75±0.36**	36.57±0.23**

Four animals in each group are used to calculate the mean±SEM. ** shows $p<0.05$ compared to the negative control group. Paracetamol (150 mg/kg).

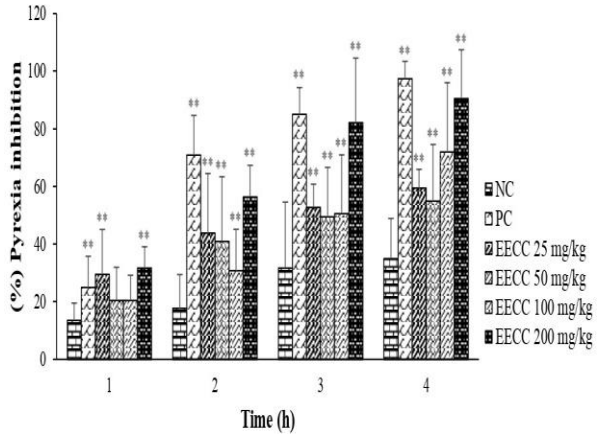

Figure 2. Antipyretic effect of EECC in rats model. EECC (25, 50, 100 and 200 mg/kg) and paracetamol (150 mg/kg) were administered for 1, 2, 3, and 4 h to reduce pyrexia. Four animals in each group are used to calculate the mean±SEM. ** shows $p<0.05$ compared to the negative control group.

In order to keep the body temperature stable, the hypothalamus controls the body's temperature by balancing heat production and loss. Fever can be triggered by a wide range of illnesses, including infection, tissue damage, inflammation, and a host of other health issues. In order to raise the temperature, the set point must be increased. This is done by generating and retaining heat. An additional benefit of vasoconstriction is that it lessens heat loss from the skin. In this way, the body matches the blood-brain temperature with the new set-point created by the hypothalamus. During fever, there is an increase in the formation of cytokines (interleukins, interferons (α,β), as well as tumor necrosis factor-alpha) [15-17]. Furthermore, these cytokines migrate to the circumventricular organs of the brain and bind to endothelial receptors on the vessel wall or interact with local microglial cells. They activate the arachidonic acid pathway upon binding, which further increases PGE2 synthesis. This pathway consists of the enzymes phospholipase A2, COX-2, and PGE2 synthase, responsible for synthesizing and releasing PGE2, which is the final mediator for the febrile response. The body temperature set-point remains high until PGE2 is present in the hypothalamus. It triggers the hypothalamus for more heat generation by minimizing heat loss through the cyclic adenosine monophosphate pathway [18, 19]. Moreover, intraperitoneal injections of peptone are widely known to induce fever in rats by increasing the production of PGs, especially PGE2, thereby raising the set-point of the thermoregulatory center in the hypothalamus [20]. It is considered a valuable experiment for screening plant materials and synthetic drugs for their antipyretic effects [21, 22]. These results indicate that oral administration of EECC significantly decreases the rectal temperature of peptone-induced fever rats. This might be due to the active compounds contained in the extract. A previous study showed that EECC contains several secondary metabolites, including polyphenols, flavonoids, alkaloids, tannins, saponins, and triterpenes [23, 24]. Furthermore, several studies have reported flavonoid compounds' antipyretic and antioxidant activities [25-27]. This compound reportedly functions by inhibiting inflammatory mediators that cause fever, including IL1β, IL6, and TNF-α [28-30]. Flavonoids have also been reported to strongly inhibit the COX-2 enzyme [31, 32]. By inhibiting the COX-2 enzyme, PGE2 synthesis will be reduced, which in turn, causes a decrease in fever temperature [33].

Conclusion

Based on the results, EECC has antioxidant effects in the DPPH model and antipyretic in peptone-induced fever rats. Meanwhile, no mortality or any major signs of toxicity was recorded for acute toxicity. This effect is due to the secondary metabolites contained, especially the flavonoid content. These findings corroborate the use of *C. costata* for the treatment of fever by traditional practitioners in North Sumatra. This implies that EECC can be an important source of natural compounds suitable for developing new treatments to treat fever.

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Conflict of interest: None

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Ethics statement: This experimental protocol was approved by the Research Ethics Commission, Universitas Padjadjaran (Number: 358/UN6.KEP/EC/2021).

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