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The beneficial effect of the ethanolic extract *Etlingera elatior* fruit on IL-1ß and caspase-3 levels in sepsis mice model

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ABSTRACT

Etlingera elatior contains various active compounds with anti-inflammatory, antioxidant, and antibacterial effects. In sepsis, endothelial dysfunction can occur due to oxidative stress and hyperinflammation. This study evaluated the effect of *E. elatior* (EE) ethanolic extract in reducing IL-1ß and caspase-3 levels in sepsis model mice. Thirty-two *Mus musculus* mice ($n = 32$) were randomly distributed into four groups ($n = 8$). Induction of sepsis was performed through intraperitoneal injection of lipopolysaccharide (LPS) 0.3 mg/kgBW. Ethanol extract of EE 4.2 mg/20 g, p.o. was given 5 days before (EE-1), 5 days after (EE-2), and simultaneously during LPS induction (EE-3). ELISA was used to measure IL-1ß and caspase-3 levels. The ANOVA was performed to test the differences of each group. Mean levels of IL-1ß ($p < 0.05$) and caspase-3 ($p < 0.05$) differed in the control group with each intervention group. The EE significantly reduced levels of IL-1ß and caspase-3 ($p < 0.05$), with the best results being before LPS induction. This study provides that EE may have a role in averting endothelial dysfunction in sepsis by lowering levels of IL-1ß and caspase-3.

INTRODUCTION

Sepsis is a life-threatening emergency due to multiple organ dysfunction resulting from systemic host dysregulation in response to infection (Gyawali *et al*., 2019). The central mechanism of sepsis is acute inflammation involving multiple organs (Hotchkiss *et al*., 2017). Data from the World Health Organization (WHO) showed that the global incidence of sepsis was 189 per 100,000 people/year with a mortality rate of 26.7%, and the mortality of sepsis patients in intensive care units was 42% (WHO, 2020). Fifteen percent of sepsis patients experienced septic shock, with a mortality rate of more than 50% (Dugar *et al*., 2020).

Sepsis pathophysiology and pathogenesis come from the reaction of infection, and bacterial infection is still the main cause (Prescott and Angus, 2018). The occurrence of infection can also be influenced by environmental factors such as air, water, food, or changes in climate and seasons. In sepsis, excessive inflammation and oxidative stress cause degranulation and release of proteases, resulting in local and systemic endothelial damage. Complement released as an immune response is known to induce endothelial dysfunction (Chang, 2019; Jacobi, 2021). Endothelial dysfunction can be used as a predictor of patients' mortality in sepsis, where endothelial dysfunction plays a role in the pathophysiology of septic shock and organ dysfunction (Boisramé-Helms *et al*., 2013). Current management of sepsis does not specifically target inflammation and oxidative stress. Therefore, effective adjuvant

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therapy is needed to reduce inflammation and oxidative stress (Lin *et al*., 2018).

The kecombrang plant (*Etlingera elatior*) is one of the plants widely found in Asia, especially in Indonesia, and has commonly been used as traditional medicine (Anzian *et al*., 2017). Kecombrang fruit contains bioactive alkaloids, flavonoids, tannins, and terpenoids (Juwita *et al*., 2018; Leorita *et al*., 2018). Many experiments have shown that *E. elatior* (EE) has extensive benefits, such as anti-inflammatory (Srey *et al*., 2014), antioxidant (Isyanti *et al*., 2019), antibacterial for gram-negative or gram-positive microbes (Sahidin *et al*., 2019), and also antihyperglycemic and antihyperuricemic effects (Dewi *et al*., 2016; Tundis *et al*., 2010). A study by Srey *et al*. (2014) showed that EE extract could act as an anti-inflammatory by suppressing nitric oxide production by up to 91% at concentrations up to 100 g/ml (Srey *et al*., 2014). At doses of 300–400 mg/kgBW, ethanol extract of kecombrang fruit has the potential to act as an immunomodulator (Wahyuni *et al*., 2018).

Sepsis is still a health problem with high mortality rates. Prompt and appropriate treatment can improve the prognosis in sepsis patients (Cecconi *et al*., 2018). An *in vivo* study is needed to assess the potential anti-inflammatory and antioxidant effects of the ethanol extract of EE fruit in the treatment of sepsis. The aim of this study was to identify and evaluate the potential of local plants, namely ethanol extract of kecombrang fruit in reducing IL-1ß and caspase-3 levels in experimental animal models.

MATERIAL AND METHODS

The use of experimental animals in this study has complied with the 3R principles according to the provisions of the National Center for the Replacement, Refinement, and Reduction of Animals in Research (NC3Rs) and has been ethically approved by the Health Research Ethics Committee of Dr. Moewardi General Hospital (serial number: 477/IV/HREC/2021). This study was conducted at the Laboratory of Food and Nutrition Study of PAU, Universitas Gadjah Mada, Yogyakarta, and the Biomedical Laboratory of Universitas Sebelas Maret, Surakarta.

Experimental animals

Adult male Balb/C strain 3–4 months old and weighed 20–30 g were used in this research. Male mice were obtained and kept in experimental animal care at PAU Universitas Gadjah Mada, Yogyakarta. Throughout the observation, all animals were kept at room temperature of 32°C with light controlled in 12-hour light:12-hour dark cycle, fed standard with BR 1 diet according to body weight, and given water *ad libitum* for 7 days.

Preparation of extract

EE fruits were obtained from Langkaplancar, Pangandaran, and Jawa Barat. Extraction is conducted by maceration methods. The chemicals used are 70% ethanol. The fruits were peeled, washed, and dried, then crushed with a blender. The first maceration process was conducted for 24 hours, followed by another 2 hours at room temperature. The sample was centrifuged at 4°C at a 4,200 rpm speed for 20 minutes. The filtrate obtained was put into an extraction flask and evaporated with a rotary evaporator at 50°C. The extract was then tested using high-performance liquid chromatography examination (Farida and Maruzy, 2016). According to an analysis of the levels of vanillic acid and ethanol extract, 1 gram of ethanol extract of E. elatior fruit contained 255 mg of vanillic acid).

Experimental design

The research laboratory with post-test only group design was used in this study. The number of *Mus musculus* mice in this study was calculated using the Federrer formula to get at least 5 mice per group for 4 groups. The mice were divided into four groups at random (n = 8 per group). Each group of mice received an intraperitoneal injection of 0.3 mg/kgBW lipopolysaccharide (LPS) to induce sepsis.

Control group: sepsis control mice received LPS alone.
EE-1 group: given ethanol extract of EE starting from 5 days before LPS induction.
EE-2 group: given ethanol extract of EE 5 days after LPS induction.
EE-3 group: given ethanol extract of EE simultaneously LPS induction.

Each experimental animal received a daily dose of 4.2 mg/20 g ethanol extract of EE. All treatments were administered orally every day until 7 days before the sacrifice. The IL-1β level was measured before the mice were killed and caspase-3 expression was examined after mice were sacrificed.

Measurement of IL-1β levels and caspase-3 expression

The venous blood sample of each mice was collected into a separated serum tube before the sacrificed day. The research protocol of IL-1β and Caspase-3 levels (Sigma Aldrich, USA) used the ELISA method and were conducted as a manufacturer's instruction. Each plate contained 100µl of mice serum that has been diluted with serum diluent (1:50) and incubated at 37°C for 45 minutes. A conjugate solution and 100µl of ABTS peroxidase were also added to the plate. Each plate then received a 25 µl stop solution treatment. If the difference in optical density (OD) between the (+) and (−) is ≥0.300 at a wavelength of 405 nm, the result is positive.

Statistical analysis

Statistical analysis in this study was done using SPSS version 22.0 for Windows. A descriptive analysis was conducted to determine the characteristics of the research sample. The numerical data were tested for normality with Shapiro–Wilk and homogeneity of variance with Levene's test. The ANOVA *F*-test was used to determine differences in each group of data with a normal and homogeneous distribution, followed by the post-hoc least significant difference test to determine the difference in mean between groups. Meanwhile, for data that is not normally distributed, the Kruskal–Wallis test is carried out, followed by the Mann–Whitney test.

Table 1. Effects of the ethanol extract of EE fruit on caspase-3 and IL-1ß levels in various treatment preparations.

Treatment	Caspase-3 levels	IL-1ß
EE-1	2.70 ± 0.22	0.23 ± 0.04
EE-2	5.33 ± 0.22	0.55 ± 0.03
EE-3	3.86 ± 0.31	0.42 ± 0.04
Control	7.83 ± 0.29	0.99 ± 0.07
p-value	<0.001*	<0.001*

* Significant $p < 0.05$.

RESULT

Effects of the ethanol extracts of Kecombrang fruit on caspase-3 levels in sepsis model

Table 1 shows the ANOVA test results for differences in caspase-3 levels in the EE-1, EE-2, EE-3, and control groups. According to Table 1, an ethanol extract of kecombrang fruit at 4.2 mg/20 g significantly (p = 0.001) reduced caspase-3 levels (Fig. 1), with the best results in the EE-1 group. Table 2 shows significant difference in caspase-3 levels in the EE-1, EE-2, and EE-3 groups, and partially in the control group ($p < 0.05$). Based on the description above, it is clear that the ethanol extract of kecombrang fruit is effective in reducing caspase-3, with the best results in the group (EE-1) treated with the extract 5 days before LPS.

Effects of the ethanol extract of Kecombrang fruit on IL-1ß levels in sepsis model

Table 1 shows the effect of the ethanol extract on the IL-1ß levels in the EE-1, EE-2, EE-3, and control groups. The ethanol extract significantly (p = 0001) reduced IL-1ß levels in all the groups (Fig. 2), with the best results in the EE-1 group. Table 2 shows significant differences in IL-1ß levels in the EE-1, EE-2, and EE-3 groups and partially in the control group ($p < 0.05$). Based on the result, it is clear that the ethanol extract of kecombrang fruit can reduce the IL-1ß levels and that it can do so more effectively when administered prior to LPS (EE-1).

DISCUSSION

Sepsis is a medical emergency induced by a systemic immune response to infection that can lead to septic shock, where bacterial infections are still the main cause of sepsis (Dugar *et al*., 2020; Gyawali *et al*., 2019; Hotchkiss *et al*., 2017; Prescott and Angus, 2018). A mortality rate above 50% is associated with sepsis and septic shock (Dugar *et al*., 2020). In sepsis, severe endothelial cell dysfunction may lead to multiorgan disorders' progression (Ince *et al*., 2016). The release of proinflammatory cytokines such as TNF-a, IL-1, and Il-6 from macrophages may exacerbate systemic infection and endothelial dysfunction in sepsis (Aziz *et al*., 2012).

In septic conditions, endothelial apoptosis is involved in endothelial injury and dysfunction. The Shioiri *et al*. (2009) research found that LPS in sepsis induces a significant increase in caspase-3 activity (Shioiri *et al*., 2009). The main executor of the apoptotic process is caspase-3. Nonsurvivor septic patients were recorded to have higher serum caspase-3 concentrations than survivors. Compared to healthy ones, septic patients have higher caspase-3 in their lymphocytes, spleen samples, and plasma (Lorente *et al*., 2018).

IL-1ß is known to cause vasodilation and hypotension and increase integrin synthesis, leading to the adherence of leukocytes and also stimulates the expression of intercellular adhesion molecules to promote neutrophil adhesion to the endothelial cells (Namas *et al*., 2012; Nasronudin, 2011). This phenomenon may trigger endothelial leakage and lead to septic shock. Thus, IL-1ß and caspase-3 can be the apparent markers of endothelial dysfunction in sepsis (Aziz *et al*., 2012; Luan *et al*., 2015; Namas *et al*., 2012).

In this study, the level of caspase-3 expression was reduced in subjects who received the ethanol extracts treatment at various times, with treatment group 1 (EE-1) having the lowest caspase-3 value. IL-1ß also significantly decreased compared to the baseline value (control group). The EE-1 had the lowest IL-1ß values. It shows that administering EE 5 days prior to mice-induced sepsis protects against endothelial dysfunction by inhibiting caspase-3 and IL-1ß expression. In sepsis, decreased caspase-3 expression and IL-1ß levels reduce the likelihood of endothelial dysfunction. This is consistent with the findings of Juwita et al. (2020), who found that a 1,000 mg/kgBW dose of EE extract reduced the expression of nuclear factor-B (NF-kB) in gastric ulcer model rats (Juwita *et al*., 2020).

Kecombrang fruit extract contains bioactive compounds such as vanillic acid that plays a role in fighting inflammation.

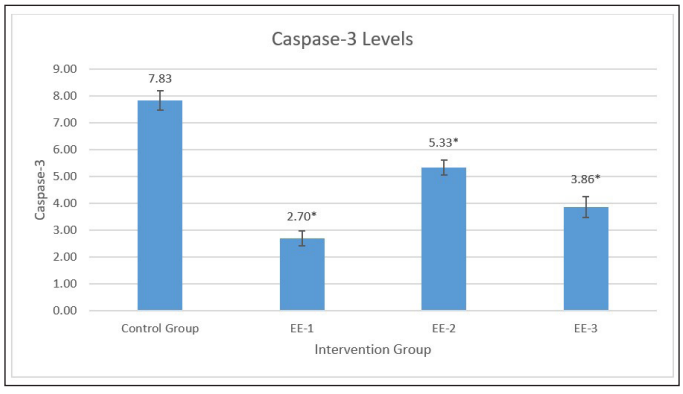

Figure 1. Description of caspase-3 levels in each treatment preparation. EE extract decreased caspase-3 in experimental groups. Data represent the mean of three independent experiments and the best results in the group (EE-1) treated with the extract 5 days before LPS (EE-1 mean: 2.70, *$p < 0.001$).

Table 2. Post-hoc test of caspase-3 and IL-1ß levels in the EP1 group, the EP2 group, the EP3 group, and the control group.

Treatment	Caspase-3 levels p-value			IL-1ß p-value		
	EE-1	EE-2	EE-3	EE-1	EE-2	EE-3
EE-2	<0.001*			<0.001*		
EE-3	<0.001*	<0.001*	<0.001*	<0.001*	<0.001*	<0.001*
Control	<0.001*	<0.001*	<0.001*	<0.001*	<0.001*	<0.001*

* Significant $p < 0.05$.

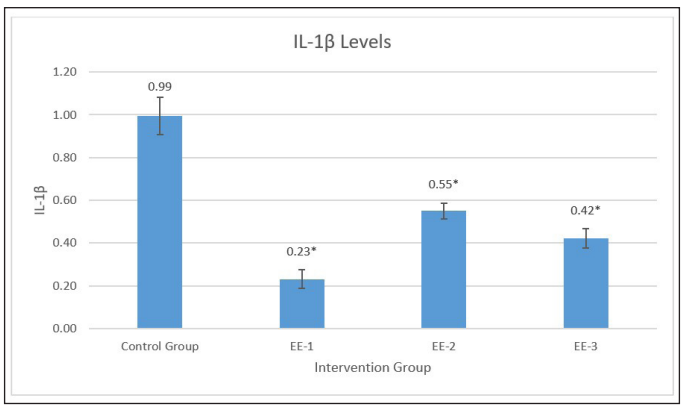

Figure 2. Description of IL-1ß levels in each treatment preparation, EE extract decreased caspase-3 in experimental groups with the best results in the group (EE-1) treated with the extract 5 days before LPS (EE-1 mean: 0.23, *$p < 0.001$).

The inflammatory process is believed to be inhibited through the suppression of cyclooxygenase-2 expression and the inhibition of transcriptional activation (NF-kB) and caspase-1 (Ernilasari *et al*., 2021; Hu *et al*., 2022). In addition, the alkaloids, phenolics, and flavonoids of kecombrang fruit extract can inhibit the growth of *Staphylococcus aureus* and *Escherichia coli* bacteria at a concentration of 2% through cell wall destruction (Ernilasari *et al*., 2021; Ghasemzadeh *et al*., 2015). Based on the results of the study, the potential of EE to inhibit bacterial growth is shown. Administration of EE before the induction of sepsis may have a protective effect on the endothelium by suppressing bacterial growth. Sepsis will affect various organs, and endothelial cells are the first to be exposed due to the inflammatory cascade by various cytokines (Dolmatova *et al*., 2021). It was reported that 48.4% of septic patients based on the Sepsis-3 criteria had bacteremia (Yu *et al*., 2022)

In sepsis, there is also an increase in the activity of the enzyme NADPH (nicotinamide adenine dinucleotide phosphate) oxidase, which synthesizes reactive oxygen species (ROS) in blood vessels (Heerebeek *et al*., 2002; Wu *et al*., 2007). Increased ROS triggers an increase in caspase-3 and causes apoptosis. Flavonoids can inhibit the action of the NADPH oxidase enzyme and capture ROS (Yousefian *et al*., 2019). Inhibition of the expression of NADPH oxidase, NF-kB, and IL-1β can reduce the apoptotic process which is characterized by a decrease in caspase-3 levels and prevent endothelial damage. Bacterial infection can trigger apoptosis in endothelial cells (Dolmatova *et al*., 2021; Ince *et al*., 2016). EE plant-containing flavonoids may have an anti-inflammatory effect and inhibit endothelial cells apoptosis which can be the target of therapeutic development of sepsis.

Further study awaits to determine the exact mechanism of EE suppressing the level of caspase-3 and IL-1β and also the effect of the daily routine of EE administration. To determine the effective dose, studying different doses of EE is necessary to prevent endothelial damage. This study will benefit the development and utilization of EE ethanolic extract and provide reliable evidence for its future clinical applications for sepsis treatment.

CONCLUSION

The intervention of kecombrang fruit ethanol extract on caspase-3 and IL-1β levels in various preparation treatments showed that kecombrang fruit ethanol extract (4.2 mg/20gr) can reduce caspase-3 and IL-1β, with the best results in the group given ethanol extract before LPS induction. This demonstrates that kecombrang extract given before induction can significantly reduce caspase-3 and IL-1β expression levels, demonstrating the potential benefits of kecombrang extract in averting endothelial dysfunction in sepsis. As a result, kecombrang extract may be utilized as an adjuvant therapy in treating sepsis.

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AUTHOR CONTRIBUTIONS

All authors made substantial contributions to the conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agreed to be accountable for all aspects of the work. All the authors are eligible to be an author as per the International Committee of Medical Journal Editors (ICMJE) requirements/guidelines.

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

ETHICAL APPROVALS

This study have been ethically approved by the Health Research Ethics Committee of Dr. Moewardi General Hospital (serial number: 477/IV/HREC/2021).

DATA AVAILABILITY

All data generated and analyzed are included in this research article.

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