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Evaluation of antipyretic activity of *Echinometra mathaei* from sabang nanggroe aceh darussalam

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Abstract
The potential of marine resources that have not been much explored is sea urchin (*Echinometra mathaei*), which is shown to have high antioxidant activity. High antioxidant activity has a potential correlation with analgesic, antipyretic and anti-inflammatory activities. The study aims to determine the antipyretic activity of *Echinometra mathaei* (EM) in Balb/c mice as an animal model. This study consisted of the extraction of EM with 70% ethanol and antipyretic activity assay on albino mice which induced 10% peptone (s.c). Thirty albino mice were divided into 6 groups i.e: negative control group, positive control group, paracetamol group, extract EM 100mg/kg BW, extract EM 200mg/kg BW, extract EM 400mg/kg BW. The body temperature was observed for 1 h after extract was given p.o. The results showed that all the dosage of EM extract could reduce the elevated body temperature of the mice and the doses of 200 mg/kg BW and 400 mg/kg BW showed no significant difference with paracetamol 65 mg/kg BW ($P < 0.05$). Conclucion of the research was the extract of Echinometra mathaei has antipyretic activity at the doses of 100 mg, 200 mg, and 400 mg/Kg BW.

Keywords: antipyretic; *Echinometra mathaei*; peptone ınduced; sea urchin; mice

Introduction

Pyrexia or fever is the body's defense mechanisms of action which increases the body temperature above normal. The normal body temperature ranges between 36.5 ° C - 37.2 ° C [1]. Fever is often experienced by children and adults. Signs and symptoms that accompany fever usually include chills, muscle aches, dehydration, and general weakness. Fever can be reduced by using fever-lowering drugs or antipyretics such as paracetamol, ibuprofen, and aspirin [2]. Antipyretics are used to help restore the setpoint temperature to normal conditions by inhibiting the synthesis and release of Prostaglandin E2, which is stimulated by endogenous pyrogens in the hypothalamus [3]. But of most synthetic drugs (chemical drugs) have side effects such as ulcers, duodenal ulcers, kidney disorders, and liver damage is the effect of using antipyretic-analgesic drugs [4].

Sea urchins, which are included as echinoderm phylum, have the same characteristics as sea cucumbers, and sea star. They have round shape bodies, which are coated with a strict shell and full covered with many sharp spines for their protection [5]. Sea urchin is one of the fisheries commodities that deserve to be developed. Sea urchins were known for their economic value, the body part consumed in the gonad, or the egg. This organism can be used as a nutritious food source. Omega-3 fatty acids in the gonads of sea urchins are efficacious for lowering cholesterol levels in the body. Sea urchin gonads also contain amino acids that are quite complete for growth and human health [6].

Sea urchins are known to have anti-inflammatory, antioxidant, and anticancer activities. The antioxidant activity of polyhydroxy naphthoquinone isolated from sea urchin showed strong anti-radical activity against hydrogen peroxide, radical superoxide anions, and DPPH [7, 8]. High antioxidant activity of echinochrome A, also found from the isolation of S. Mirabilis [9]. These natural antioxidants capable of scavenging free radicals play a significant role in the prevention of vascular diseases and some types of cancer [10]. Free radicals, which have one or more unpaired electrons in their outer orbital, consist of superoxide anion ($O2^{\bullet -}$), alkoxy (RO•), peroxyl (ROO•), hydroxyl (HO•), and nitric oxide. Oxygencentred free radicals are, sometimes known as Reactive Oxygen Species (ROS) [11], which attack macromolecules such as lipids, proteins, enzymes, DNA, and RNA [12]. Scavenging of ROS leads to a reduction of oxidative stress of organisms and prevents some chronic and degenerative diseases such as aging, stroke, diabetes mellitus, cancer, cardiovascular and neurodegenerative complications [13]. As a result, antioxidants that can scavenge ROS are likely to help with these issues [9]. According to Soleimani [14], the methanol extract of sea urchin has the same mechanical action as aspirin as an anti-inflammatory analgesic, and antipyretic drug through inhibition of the activity of the enzyme cyclooxygenase-2 (COX-2) which inhibits prostaglandin (PG) biosynthesis which causes inflammation, swelling, pain, and fever [15].

Materıals and Methods

Materials

Echinometra mathaei, Balb/C mice (18-25 g) was collected from the Veterinarian Center in Surabaya, Paracetamol® tablets containing Paracetamol were generously provided by Bernopharm Pharmaceuticals, Peptone water (Sigma), dan ethanol 70% with pharmaceutical grade. Basal ear temperatures were measured by infrared technology from Braun digital ear thermometer (Thermoscan 7 IRT 6520).

Sample Preparation

Sea urchin (*Echinometra mathaei*) was collected from We Island, Sabang, Nangroe Aceh Darussalam, Indonesia, at depths of 5-10 m under the sea level during Oktober 2018. The sample has been authenticated by the Biology Service Unit, Faculty of Sains and

Technology, Airlangga University Surabaya. The shell and gonad of Echinometra mathaei were not separated, mixed, shaded, dried, and powdered into a dried coarse powder. The sample powder was then extracted with 70% ethanol by using solvent replacement (1:10), for maximizing the extraction through maceration.

Animal Experimental Design

The Antipyretic activity was determined by Heni Purwitasari modified method [16]. The mice have fasted overnight before the experiments, but they were provided with water ad libitum. The mice were divided into six groups, and each group consists of five mice. Basal ear temperatures were measured by an infrared ear thermometer. The normal body temperature of mice was ± 36,5^{0}C. The mice were administered 10% peptone water subcutaneous induction and 2h later, ear temperatures of the hyperpyrexic mice were measured. The animal handling for this research was performed by the regulations of The Institutional Animal Ethics Committee (Approval code: 005/HC/EC/F/ KEPUHT/2019).

The Echinometra mathaei extracts (100, 200, and 400mg/kg BW), saline water, and paracetamol (65 mg/kg BW) were orally administered to the mice. The ear temperatures were measured every 5 min up to 1h. The temperature after 1h treatment was compared with hyperpyrexia temperature.

Statistical Analysis

The mean and standard error of the mean were used to present the findings. The data was analyzed using SPSS 22.0 program. A one-way ANOVA was used to compare the data between gropus, followed by a post-hoc Least Significant Difference test. At P<0.05, values were considered statistically significant.

Results and Dıscussıon

The peptone was used to initiate the pyrexia. The peptone-induced pyrexia is due to the PGE2 production which sets the thermoregulatory center at a higher temperature. The hypothalamus PGE2 was produced by COX2 as the principal downstream mediator of fever [17]. Peptone can produce an increased body temperature in mice from normal (36.60 ± 0.19 ^{0}C) to 37.25 ± 0.25 ^{0}C after 1-2 h of injection. Paracetamol has potent antipyretic and analgesic activities with minimal anti-inflammatory activity. It may selectively inhibit specific COX isoform in the CNS to inhibit PGE2 synthesis to achieve its antipyretic effect, but does not influence body temperature when it is elevated by other factors such as exercise or increase in ambient temperature. The possible mechanism for the antipyretic activity of the ethanolic extract is due to the inhibition of PGE2 synthesis [18]. Paracetamol as a standard drug was reduced the body temperature, from 37.04 ± 0.12^{0}C to 36.30 ± 0.12^{0}C after 1 h of drug treatment as well as shown in the administration of extracts that reduce fever after 1 h of oral administration. The extract of Echinometra mathaei possessed antipyretic activity to peptone-induced hyperpyrexia in mice, and their activities are no significant difference to paracetamol at the dose of 200 mg/kg BW and 400 mg/kg BW (Table 1). The antipyretic activity from the Echinometra mathaei was dose-dependent, the higher dose will produce a higher activity on peptone-induced hyperpyrexia in mice.

Table 1: Results of Antipyretic Activity Assay

Groups	T basal (^{0}C)	T after induction (^{0}C)	T_{60} After treatment (^{0}C)	Δt (^{o}C)
Negative control	36.04 ± 0.40	-	36.28 ± 0.18^b	+ 0.36 ± 0.23
Positive control	36.38 ± 0.13	37.10 ± 0.39	37.84 ± 0.34^a	+ 0.74 ± 0.65
Paracetamol 65mg/kg BW	36.68 ± 0.23	37.04 ± 0.12	36.30 ± 0.12^b	- 0.74 ± 0.20
EM 100mg/kg BW	36.68 ± 0.26	37.54 ± 0.34	36.94 ± 0.36^a	- 0.60 ± 0.40
EM 200mg/kg BW	36.68 ± 0.18	37.22 ± 0.18	36.34 ± 0.11^b	- 0.88 ± 0.24
EM 400mg/kg BW	36.74 ± 0.15	37.34 ± 0.22	36.44 ± 0.17^b	- 0.90 ± 0.21

Note: superscript (^{a}) indicates significant differences between negative control, superscript (^{b}) indicates significant differences between positive control group (P < 0.05)

The hypothalamus governs the set point at which body temperature is maintained, which necessitates a careful balance between heat generation and heat loss.

It is well established that fever is mediated by the release of prostaglandins in the hypothalamus, which results in increased heat production and decreased heat loss leading to pyrexia [19]. In fever, this set point is elevated and drugs like paracetamol do not influence body temperature when it is elevated by factors like exercise or an increase in ambient temperature.

The antipyretic activity of Echinometra mathaei may be due to the inhibition of prostaglandin synthesis.

Conclusıon

The Extract of Echinometra mathaei has antipyretic activity at all doses. The doses of 200 mg/kg BW and 400 mg/kg BW showed no significant difference with paracetamol 65 mg/kg BW. The antipyretic activity of Echinometra mathaei was predicted as a hypothesis of this research.

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