ANDALIMAN FRUIT EXTRACT (ZANTHOXYLUM ACANTOPHODIUM) AND IT'S EFFECT ON PREECLAMPSIA AS ANTI-INFLAMMATORY

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INTRODUCTION

One indicator a country's health status is the maternal mortality rate (MMR). According to the World Health Organization, the global maternal mortality rate in the world amounted to 289,000 in 2013. The World Health Organization (WHO) in 2013 estimated that around the world every day around 800 women die from complications of pregnancy, childbirth, and the puerperium [1]. About 99% of maternal deaths occur in developing countries, including in Indonesia. The ratio of maternal deaths in developing countries is around 240 per 100,000 live births and in developed countries around 16 per 100,000 live births [2].

Hypertension in pregnancy is one of the causes of maternal death and ranks third in the cause of maternal death in Indonesia. Hypertension in pregnancy occurs in about 10% of all pregnant women throughout the world. Hypertension in pregnancy accounts for more than 60,000 maternal deaths worldwide each year [3, 4].

Preeclampsia is a special pregnancy syndrome that can affect the entire organ system. The criteria for preeclampsia is hypertension that arises after 20 w/ gestation with or without proteinuria. Preeclampsia occurs in about 2-8% of all pregnancies [4]. According to data from the National Vital Statistics Report, preeclampsia occurs in 1 per 2000 births. The frequency of preeclampsia in Indonesia is around 3-10% [5]. In Indonesia, severe preeclampsia and eclampsia are ranked third in the causes of maternal mortality in Indonesia, as many as 1.5 percent-25 percent while infant deaths range from 45 percent to 50 percent [6].

Preeclampsia is known in North Sumatra and is widely used in typical Batak dishes. This plant is used to eliminate the smell of fish and raw meat due to its strong odor. This plant has been reported to have anti-inflammatory and antioxidant activity [7]. Several studies have been conducted on the benefits of Andaliman fruit, including preservatives, medicinal ingredients and supplements, and vegetable pesticides. Currently Andaliman extract is widely used as a food supplement because it is believed to increase endurance. The contents in Andaliman such as neolignan, alkaloids, geranyl acetate, amides, and benzoic acid have high potential for the treatment of chronic inflammatory diseases [8]. In Yanti's study of macrophages induced by lipopolysaccharides, triggering the release of inflammatory cytokines, dose-dependent Andaliman administration (2.5 and 10 µg/ml) appeared to inhibit the expression of TNF-α, IL6, and inhibit the expression of protein and mRNA activity of MMP-9 in macrophages compared with a control group that examined gelatin zymografi, w estern blot, and RT-PCR. This causes the induction blockage of inflammatory enzymes so that the oxidative stress process is inhibited [9].

MATERIALS AND METHODS

Research has been conducted checks of blood pressure, MAP, proteinuria, levels of TNF-α, IL6, with the research design quasi-experimental laboratory rat/mice (Rattus norvegicus) pregnant females who administered the extract Andaliman (Zanthoxylumacanthophodium) at a dose of 100 mg and 200 mg per day with the ELISA method for 4 groups of rats, each group consisting of 6 subjects so that the number of samples needed was 24 animals. The research conducted in July-October 2019. The research sample is part of the study population that meets the inclusion and exclusion criteria by using the Postest Only Control Group Design.

CONCLUSION

This study proves that there are anti-inflammatory effects possessed by the extract of Andaliman (Zanthoxylum acanthophodium), thus showing a decrease in proinflammatory cytokine levels, namely TNF-α, IL6. This study also has a good clinical outcome after administering Andaliman extract (Zanthoxylum acanthophodium), where there are improvements in blood pressure, cystole-diastole, MAP and decreased urinary protein in research subjects with preeclampsia.
RESULTS

The experimental animals used in this study were 24 white Wistar white mice (*Rattus norvegicus* sp) 10-week-old females who met the inclusion and exclusion criteria. Then female and male *Rattus Norvegicus* mice were put together in one cage and kept for one night at a ratio of 1:1. The diagnosis of pregnancy is obtained by the presence of vaginal spermatozoa /vaginal plugs and is counted as pregnancy day 0. *Pregnant* female *Rattus Norvegicus* rats are grouped into 4 groups randomly. On the 1st day of pregnancy, all the samples are divided into four groups, namely: (1) Group 1, negative control (normal), pregnant mice were not given any treatment in general, given excessive eating and drinking (ad libitum) in their cages. (2) Group 2, the treatment group is pregnant mice given LPS injection on day 5 of pregnancy on the basis of day 8 of pregnancy trophoblast invasion was started, in order to become a model of preeclampsia mice but were not given andaliman (*Zanthoxylum achatnopus*). (3) Group 3, the treatment group is pregnant mice given LPS injection on day 5 of pregnancy on the basis of day 8 of pregnancy trophoblast invasion was started, in order to become a preeclampsia model mice and given andaliman (*Zanthoxylum achatnopus*) at a dose of 200 mg once daily. For 15 d. (4) Group 4, the treatment group namely pregnant mice given LPS injection on day 5 of pregnancy on the basis of day 8 of pregnancy trophoblast invasion was started, in order to become a model of preeclampsia mice and given andaliman (*Zanthoxylum achatnopus*) at a dose of 800 mg once daily for 15 d.

Table 1: Trial group distribution

| Group          | F   | %  |
|----------------|-----|----|
| Control-(K-)   | 6   | 25.0 |
| Control+(K+)   | 6   | 25.0 |
| Andaliman 200 (P1) | 6   | 25.0 |
| Andaliman 800 (P2) | 6   | 25.0 |
| Total          | 24  | 100.0 |

In groups 2, 3, and 4 on the 5th day of pregnancy the intravenous LPS injection was given to the tail to become a model of preeclampsia. After that, monitoring of systemic blood pressure in mice in the morning (9:00 to 10:00) was evaluated every three days. Providing andaliman (*Zanthoxylum achatnopus*) in groups 3 and 4 was given immediately after an increase in systemic blood pressure in mice. Providing andaliman (*Zanthoxylum achatnopus*) orally administered according to the dose of each group every day until the 15th day with the amount of fluid that was given was still within the recommended maximum volume of fluid in mice as much as 5 ml/kg. The procedure of feeding the mice is done first by immobilizing the mice by gently holding the loose skin area between the neck and back of the back so that the rat does not feel threatened. Then the distance between the oral cavity and the xiphoideus process is measured as the length of the gavage to be entered. *Oral gavage* is then connected to a syringe containing andaliman at the dose of each treatment group, then inserted from the left side of the mouth between the front teeth with diastema following the hard palate. When the gavage needle reaches the back of the mouth, the rats head is slightly bent back and pressure is applied to the gavage so that the esophageal position is straight with the stomach. Gavage must be moved without pressure by following the force of gravity along the esophagus to the measured length. If gavage enters the respiratory tract, mice will have difficulty breathing. If the mark is not present, a slow solution can be injected to prevent regurgitation. After administration of the extract is complete, the gavage needle is removed slowly in the opposite direction to the direction of the insertion of the gavage needle [10]. On the 16th day, terminations were made to the four groups.

Table 2: Differences in IL-6 levels

| Mean | Median | SE | SD | 95% CI | p     |
|------|--------|----|----|--------|-------|
| K-   | 16.7   | 16.7 | 3.5 | 8.5    | 7.8-25.7 | <0.001 |
| K+   | 67.5   | 69.9 | 3.5 | 8.5    | 58.6-76.4 |
| P1   | 18.8   | 21.5 | 3.5 | 8.5    | 9.9-27.7  |
| P2   | 21.1   | 23.8 | 3.4 | 8.3    | 12.4-29.9  |

The mean levels of IL-6 showed a high of 67.5 in the group of rats with preeclampsia, whereas in the group of normal mice got pregnant premises mean levels of IL-6 at 16.7. In the group of mice that received the treatment showed that the average levels of IL-6 in group P1 is 18.8 and P2 group of 21.1. This shows a decrease in the average level of IL-6 in the administration of exalactandaliman. Based on the analysis, it was found that there were differences in the mean levels of IL-6 in the study group (*p*<0.001).

Table 3: Differences in TNF-α levels

| Mean  | Median | SE | SD  | 95% CI  | p     |
|-------|--------|----|-----|--------|-------|
| K-    | 84.4   | 85.8 | 3.3 | 8.1    | 76.0-92.9 | <0.001 |
| K+    | 109.7  | 111.1 | 3.3 | 8.0    | 101.3-118.1 |
| P1    | 90.1   | 91.4 | 3.2 | 7.9    | 81.8-98.4  |
| P2    | 95.1   | 96.4 | 3.3 | 8.0    | 86.6-103.5  |

The mean TNF-α value was highest in the preeclampsia (K+) group of 109.7, whereas in the normal pregnant group (K) the TNF-α value was 84.4. In the treatment group P1, the mean TNF-α levels were 90.1 and 95.1 in the P2 group. This shows that the administration of andaliman extract reduced the average TNF-α level in preeclampsia mice both at a dose of 200 mg and a dose of 800 mg. Based on the analysis, it was found that there were differences in the mean TNF-α levels in the study group (*p*<0.001).

DISCUSSION

TNF-α induces the occurrence of oxidative damage due to destabilizing the flow of electrons inside the mitochondria causing release Oxidative free radicals and the formation of peroxides that make cell damage endotherial. TNF-α stimulates the production of angiotensin II in the reproductive tract women and IL-6 regulate levels of angiotensin II type 1 receptors in the muscles vascular.

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CONCLUSION

Andaliman has been shown to reduce TNF-α levels in preeclampsia mice.

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Nil

AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

CONFICT OF INTERESTS

The authors declare that this research was conducted without any commercial or financial relationship that could be seen as a potential conflict of interest

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