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The Effect of Red Ginger Extract on Tnf-α and Malondialdehyde Serum Level

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ABSTRACT: Pseudomonas aeruginosa is the main pathogen causing nosocomial infections in hospitals, also can infect open wounds, combustio and necrotizing pneumonia. Several plant studies show the presence of antioxidants, one of them is red ginger. Research shows that red ginger extract contains the bioactive components gingerol and shogaol which have antioxidant and antimicrobial properties. The purpose of this research is to determine the effect of red ginger extract on TNF-α and serum malondialdehyde levels in rats infected with Pseudomonas aeruginosa bacteria. This study uses an experimental research design with Post Test Only Control Group Design. The research subjects were 30 wistar rats which were randomly divided into 5 groups. K (-) group of mice without *P.aeruginosa* infection. K(+) group of rats infected with P. aeruginosa 108 CFU per head without red ginger extract. P1, P2 and P3 were infected with *P.aeruginosa* and were given red ginger extract at a dose of 20mg, 40mg and 80mg/KgBB/day for 7 days. Day 8 examination of TNF-α and MDA levels. The results of the One Way Anova test showed a significant difference in TNF- levels and MDA levels with p value = 0.000. The mean levels of TNF- in groups K(-), K(+), P1, P2, P3 were 5.76, 17.89, 12.29, 9.03, 7.07 and the mean MDA levels were 1.33, 11.10, 5.09, 3.87, 3.00. Tukey's test results showed TNF-α levels between groups had a significant difference in all groups (p=0.000) and a significant difference also in MDA levels (P=0.000). Red ginger extract had an effect on decreasing TNF-α and serum MDA levels in rats infected with *Pseudomonas aeruginosa*.

KEYWORDS: Red ginger, Pseudomonas aeruginosa, TNF-α, MDA

I. INTRODUCTION

Pseudomonas aeruginosa is the main pathogen causing nosocomial infections in hospitals.1 The increased incidence of nosocomial infection by *Pseudomonas* aeruginosa in patients at the hospital was followed by an increase in the incidence of resistance to various antibiotics such as *β-lactam*, *ciprofloxacin*, *tobramycin* and *colistin* (Ervina et al., 2017). Resistance to antibiotics can lead to a long healing time, increase the risk of death, increase *carriers* in the community, increase the number of resistant bacteria and extend the hospital stay (Utami, 2012). High ROS will cause conditions of excessive oxidative stress characterized by the presence of Malondialdehyde (MDA) which is formed from the process of lipid peroxidation. *Tumor Necrosis Factor* (TNF-α) is the main cytokine in the acute inflammatory response (Bara et al., 2020). Severe infections can trigger the production of TNF-α in large quantities and cause systemic reactions (Ali et al., 2020).

Red ginger is widely used as a raw material for medicine because it has a higher content of oleoresin and essential oils compared to other gingers (Sadikim et al., 2018). Red ginger extract contains the bioactive components gingerol and shogaol which are antioxidants and antimicrobial (Prastiti et al., 2015). The content in red ginger is able to provide pharmacological activities, such as anti-inflammatory and antioxidant (Sitompul et al., 2020). Shogaols and gingerols is a phenolic compound that can suppress anti-inflammatory activity by suppressing proinflammatory cytokines, namely TNF-α and IL-1β (Diapati et al., 2020). In addition, gingerol is able to inhibit ROS by inhibiting xanthine oxidase mechanism so that free radicals are not formed. Reducing free radicals inhibits lipid peroxidation thereby reducing serum MDA levels (Diapati et al., 2020). Therefore it is necessary to prove the effect of antioxidants from red ginger extract on the healing of *Pseudomonas aearuginosa* by looking at serum levels of MDA and TNFα.

II. MATERIAL AND METHODS

Research using experimental research design with the Post Test Only Control Group Design research design. This study used a sample of 30 male wistar rats which were divided into 5 groups of 6 rats each. The control group (K-) was not given treatment for *P.aeruginosa* and red ginger extract, the control group (K+) rats were infected *P.aeruginosa* 108 CFU/ml per head without being given red ginger extract. The treatment group (P1) was infected with *P.aeruginosa* 108 CFU/ml per head and given red ginger extract 20 mg/head/day for 7 days orally using a gastric tube. The treatment group (P2) was infected with *P.aeruginosa* 108 CFU/ml per head and given red ginger extract 40 mg/head/day for 7 days, the treatment group (P3) was infected with *P.aeruginosa* 108 CFU/ml per head and given ginger extract red 80 mg/head/day for 7 days. On the 8th day, TNF-α and MDA levels were examined. This study used male Wistar rats because they have many similarities with humans in terms of physiology, anatomy and conditions and symptoms in humans that can be applied to mice. Then the data is tested with SPSS. The data normality test was performed using Shapiro Wilk, the data homogeneity test was carried out with the Levene test, followed by the One Way Anova.

III. RESULT

The study of giving red ginger extract to TNF-α and serum MDA levels in male Wistar rats infected with Pseudomonas aeruginosa was carried out for 7 days. The results of the study are listed in table 1.

Table 1. Analysis of mean levels of TNF-α and serum MDA

Variable	Group					
	K (-) N=5 Mean	K (+) N=5 Mean	P1 N=5 Mean	P2 N=5 Mean	P3 N=5 Mean	Sig. (p)
Levels of TNF-α	5.76	17.89	12.29	9.03	7.07	
Std. deviation	.282	.393	.316	.736 .398	Shapiro	
Wilk	.506*	.883*	.570*	.349*	.849*	
Levene Test						.070**
One Way Anova						.000***
MDA	1.33	11.10	5.09	3.8733	3.00	
Std . deviation	.172	.451	.242 .334	.239	.954	
Shapiro Wilk	*	.561*	.534*	.577*	.667*	
Levene Test						.147**
One Way Anova						.000***
Description: *Normal P>0, 05 **Homogeneous p>0.05 ***Significant p<0.05						

Figure 1 showed that the average TNF- The lowest α was in the control group K(-), then successively followed by the third treatment group (P3), the second treatment group (P2), the first treatment group (P1), and the K control group (+). The treatment group (P3) got an average TNF- lowest α. Based on the Shapiro Wilk test, all groups of TNF- α indicates that the data is normally distributed (P > 0.05) and the homogeneity test using the Levene Test results are homogeneous (p > 0.05) so the data analysis uses the One Way Anova test. test One Way Anova showed significant differences between groups (p = 0.000).

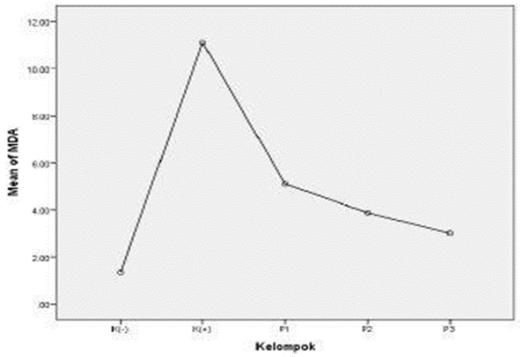

Figure 1. ***Mean of MDA serum levels***

The Effect of Red Ginger Extract on Tnf-α and Malondialdehyde Serum Levels

Figure 1 showed that the lowest mean MDA level was in the control group K(-), then followed successively by the third treatment group (P3), the second treatment group (P2), the first treatment group (P1), and the K control group (+). The treatment group (P3) got an average TNF- lowest α. Based on the Shapiro Wilk test, all TNF-α levels showed normal distribution of data (P > 0.05) and the homogeneity test using the Levene Test yielded homogeneous results (p = 0.147). Data analysis used OneWay Anova and showed significant differences between groups (p = 0.000). To find out which group is significant, a post hoc with the Tukey as presented in Table 2.

Table 2. Differences in TNF-α levels between the 2 groups using the *Tukey*

	group	Sig
K (-)	K (+)	.000*
	P1	.000*
	P2	.000*
	P3	.000*
K (+)	K (-)	.000*
	P1	.000*
	P2	.000*
	P3	.000*
P1	K(-)	.000*
	K(+)	.000*
	P2	.000*
	P3	.000*
P2	K(-)	.000*
	K(+)	.000*
	P1	.000*
	P3	.000*
P3	K(-)	.000*
	K(+)	.000*
	P1	.000*
	P2	.000*

Table 2. showed that MDA levels between groups had significant differences in all groups (p=0.000). Based on the data above, it can be concluded that administration of red ginger extract at a dose of 20 mg/head/day, 40 mg/head/day, 80 mg/head/day significantly affected the decrease in MDA levels in male Wistar rats injected with Pseudomonas aeruginosa so that the hypothesis statement can be accepted.

IV. DISCUSSION

The results obtained from the research can be seen in table 5.1. which showed the levels of TNF-α and MDA in the negative control group were 5.7650 for TNF-α and 1.333 for MDA. Meanwhile, there was an increase in the levels of TNF-α and MDA in the positive control group (after the mice were infected with the bacterium Pseudomonas aeruginosa), namely 17.8983 at TNF-α levels and 11.1017 at MDA levels. The difference in TNF-α and MDA levels in the negative control group and the positive control group is thought to be due to the treatment of mice infected with the bacterium *Pseudomonas aeruginosa*. This study is in line with research conducted by Tjahjani (2015), but in mice infected with *Staphylococcus aureus*, 24 hours later there was an increase in TNF-α levels compared to mice not infected with Staphylococcus aureus. Al-Husseini et al (2020) in a study of mice infected with the *Pseudomonas aeruginosa* gave results in the form of significantly increased levels of TNF-α and MCP-1 in plasma and organ tissue compared to the negative control group (Hasson Al-Husseini et al., 2020).

Infection Pseudomonas aeruginosa will secrete ETA toxin (exotoxin A) which can inhibit T cell activation protein synthesis to produce TNF-α, in line with this study that by inoculation of *P.aeruginosa* to mice, there is an increase in TNF-α levels. The increase in TNF-α is also associated with the activity of the transcription factor nuclear-kappa B (NF-kB) and inhibition of PPAR-γ

expression (Moser et al., 2021). Infection *Pseudomonas aeruginosa* will stimulate macrophages to release IL-12 either directly or indirectly. Interleukin-12 plays a role in the formation of Th1 cells. Furthermore, in cooperation with IL-1 and TNF-α stimulate T cells and NK cells to produce IFN-γ (Elemam et al., 2021). Interferon-γ will activate alveolar macrophages to produce various substances, including Reactive Oxygen Species (ROS) and trigger damage to cell membranes and then interfere with lipid peroxidation in cell membranes which will produce Malondialdehyde (MDA). Increased MDA is used as a marker of oxidative stress (Barrera, 2012).

The results of test observations in table 5.1. showed that the levels of TNF-α in the P1, P2 and P3 treatment groups infected with *P.aeruginosa* were lower than the positive control group. Previous research on red ginger extract proved to be able to reduce inflammatory cells including TNF-α in alloxan-induced pancreatic histopathological features of white rats (Salaramoli et al., 2022). This is in accordance with the theory that red ginger extract has active ingredients, namely shogaol and gingerol. Shogaol inhibits TNF-α because it has a function as an agonist of the Peroxisome Proliferator Activator Receptor (PPARγ agonist, while gingerol inhibits TNF-α through the mechanism of inhibition of the c-Jun NH2-terminal kinase (JNK) pathway (Mao et al., 2019). Shogaol and gingerol can reduce αα intreatment groups P1, P2, and P3. Group P3 at a dose of 80 mg/KgBW/day even reduced TNF-α levels close to the levels of group K (-). Red ginger (Zingiber officinale var rubrum) contains phenolic compounds, namely shogaol and 6- gingerol, this substance can inhibit TNF-α directly or inhibit the increase in nuclear factor kappa B (NF-KB) which is associated with the formation of proinflammatory cytokines (Mashhadi et al., 2013).

Red ginger extract was proven in research conducted by Dewi (2019) to have a significant effect on the bacterial inhibition zone and red ginger extract had the highest inhibition area against Pseudomonas aeruginosa. This study is in line with previous studies which used a combination of red ginger and reed extracts at doses of 18+40 mg and 36+40 mg to reduce serum MDA levels of OA rats. In accordance with the theory that shogaol will act as an antioxidant through the nuclear factor erythroid 2-related factor 2 (Nrf2) signaling pathway, induces the expression of several cells in the Nrf2 pathway such as MT1, HO-1 and GCLC so that it can suppress lipid peroxidation and reduce MDA levels (Axis et al., 2022). The results of the MDA examination that the researchers conducted showed a decrease in MDA levels in rats infected with *P.aeruginosa* and given red ginger extract for 7 days. The test data showed that MDA levels in the P1, P2 and P3 treatment groups infected with *P.aeruginosa* and given red ginger extract were lower than the positive control group. Red ginger extract has an antioxidant effect and reduces ROS production and lipid peroxidation. Lipid peroxidase itself will produce a substance called Malondialdehyde (MDA) (Ratriantari & Probandari, 2019).

Based on the research results obtained and the theoretical studies that have been described by the researchers above, the hypothesis that giving red ginger extract can reduce levels of MDA and TNF-α in rats infected with the bacterium *P.aeruginosa* has been proven.

V. CONCLUSION

Red ginger extract at a dose of 20 mg/head/day, 40 mg/head/day, 80 mg/head/day had an effect on decreasing TNF-α and serum MDA levels in rats infected with the bacterium *Pseudomonas aeruginosa*. Further research is needed to determine the toxic dose that can arise from red ginger extract so that a therapeutic dose range is obtained for infections caused by the bacterium *P.aerugginosa*.

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