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The Effectiveness of Garlic Extract (*Allium sativum*) against Decreased Serum Levels Tumor Necrosis Factor- α (TNF- α) in Chronic Hemodialysis Patients at Dr. Mohammad Hoesin General Hospital, Palembang, Indonesia

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ABSTRACT

Background: Chronic kidney disease (CKD) is a pathophysiological process with various etiologies resulting in a progressive decline in kidney function and generally ends in kidney failure. During hemodialysis, inflammation and activation of TNF- α and other proinflammatory cytokines occur. This inflammatory condition causes a decrease in the effectiveness of HD in reducing the mortality of patients with CKD. Garlic has the potential as an anti-inflammatory agent due to its high antioxidant content in garlic. This study aimed to determine the effectiveness of garlic extract (*Allium sativum*) on decreasing serum levels of tumor necrosis factor- α (TNF- α) in chronic hemodialysis patients at Dr. Mohammad Hoesin General Hospital, Palembang, Indonesia. **Methods:** This study is an experimental study with a randomized, controlled, double-blind trial crossover design. A total of 40 research subjects participated in this study which was grouped into treatment (garlic extract) and placebo groups. TNF- α levels were measured using the ELISA method. Data analysis was carried out using SPSS univariate and bivariate. **Results:** The results of the study showed that the administration of garlic extract was able to reduce TNF- α levels by 12.5 pg/mL, $p < 0.05$. In contrast, in the placebo group, there was an increase in TNF- α levels of 8.3 pg/mL, $p < 0.05$. **Conclusion:** Garlic extract (*Allium sativum*) is effective in reducing tumor necrosis factor- α (TNF- α) serum levels in chronic hemodialysis patients at Dr. Mohammad Hoesin General Hospital, Palembang, Indonesia.

1. Introduction

Chronic kidney disease (CKD) is a pathophysiological process with various etiologies resulting in a progressive decline in kidney function and generally ends in kidney failure. The global prevalence of chronic kidney disease is increasing gradually and is one of the major health problems in the world. The growth rate of CKD patients globally

has increased by 7% annually and will increase in line with population growth. HD (hemodialysis) is the most widely used renal replacement therapy today. However, several studies have stated that the morbidity rate of CKD patients undergoing HD is 20% per year. During hemodialysis, inflammation and activation of TNF- α and other proinflammatory cytokines occur. This inflammatory condition causes a

decrease in the effectiveness of HD in reducing the mortality of patients with CKD. There are no interventions and treatments that are effective in overcoming the inflammatory process that occurs in patients undergoing hemodialysis. Therefore, it is necessary to explore new therapeutic modalities optimally.¹⁻⁵

Indonesia is a country with the second-largest biological wealth in the world. This great biological potential has the opportunity to explore the potential of natural materials as new therapeutic modalities. Garlic (*Allium sativum*) is a natural ingredient that is very familiar to the people of Indonesia as a cooking spice. Garlic is useful not only as a cooking spice, but several studies show the potential of garlic extract in overcoming various health problems such as hypertension and diabetes mellitus. Several studies also show that garlic has the potential as an anti-inflammatory agent due to its high antioxidant content in garlic.⁶⁻⁹ This study aimed to determine the effectiveness of garlic extract (*Allium sativum*) on decreasing serum levels of tumor necrosis factor- α (TNF- α) in chronic hemodialysis patients at Dr. Mohammad Hoesin General Hospital, Palembang, Indonesia.

2. Methods

This study is an experimental study with a randomized, controlled, double-blind trial crossover design. This research was conducted at the hemodialysis installation of Dr. Mohammad Hoesin General Hospital, Palembang, Indonesia. A total of 40 research subjects participated in this study. This study consisted of two phases. In phase I, group A consisted of 20 samples who received garlic extract (hereinafter referred to as the garlic group), and group B consisted of 20 samples who received a placebo. The results of both groups were observed for 6 weeks. This is followed by a period of rest (washout) for 2 weeks.

Then in phase II, group A and group B received the alternate treatment. The inclusion criteria for research subjects were chronic hemodialysis patients who underwent routine hemodialysis twice a week with a duration of 4-5 hours each session, and more than three months and a maximum of 2 years at Dr. Mohammad Hoesin General Hospital, Palembang, Indonesia., aged ≥ 18 years - 60 years and willing to take part in the research by signing the form informed consent. This study was approved by the medical and health research ethics committee at Dr. Mohammad Hoesin General Hospital, Palembang, Indonesia.

This study conducted sociodemographic and clinical data from the study subjects. TNF- α levels were assessed using the enzyme-linked immunosorbent assay (ELISA) method. In the garlic extract group, they were given 500 mg capsules of garlic extract at a dose of 2x1 capsule per day for 6 weeks, while in the placebo group, they were given placebo 2x1 capsules for 6 weeks. Data analysis was carried out using SPSS 25 for windows software. Univariate analysis was performed to present the distribution of data frequencies for each test variable. Bivariate analysis was performed to determine the mean difference in TNF- α levels in each treatment group, with a p-value < 0.05 .

3. Results

Table 1 presents the general characteristics of the research subjects. The research subjects had an average age of 48.6 years, and the majority of research subjects were male. The majority of research subjects had senior high school education, and the majority were unemployed and self-employed. The study subjects, on average, had undergone hemodialysis for 16 months and had a normal body mass index. The majority of research subjects had comorbid hypertension.

Table 1. General characteristics of research subjects.

	Group		
	Total (n=40)	Garlic (n=20)	Placebo (n=20)
Age	48,6 (26-59)	45,5 (28-58)	55 (26-59)
Gender			
Male	23 (57,5 %)	12 (60 %)	11 (55 %)
Female	17 (42,5 %)	8 (40 %)	9 (45 %)
Education			
Primary school	2 (5 %)	-	2 (10 %)
Junior high school	9 (22,5 %)	4 (20 %)	5 (25 %)
Senior high school	19 (47,5 %)	12 (60 %)	7 (35 %)
College	10 (25 %)	4 (20 %)	6 (30 %)
Occupation			
Not working	18 (45 %)	11 (55 %)	7 (35 %)
Private	18 (45 %)	9 (45 %)	9 (45 %)
Civil servant	4 (10 %)	-	4 (20 %)
Length of HD (months)	16 (3-24)	20 (4-24)	12 (3-24)
IMT	22,52 ± 2,78	23,171 ± 2,96	21,88 ± 2,51
Less	1 (2,5 %)	-	1 (5 %)
Normal	33 (82,5 %)	16 (80 %)	17 (85 %)
Overweight	3 (7,5 %)	2 (10 %)	1 (5 %)
Obesity	3 (7,5 %)	2 (10 %)	1 (5 %)
Comorbid			
Hypertension	26 (65 %)	14 (70 %)	12 (60 %)
DM type 2	4 (10 %)	2 (10 %)	2 (10 %)
Hypertension and DM type 2	10 (25 %)	4 (20 %)	6 (30 %)

Table 2. Comparison of serum TNF- α levels and its changes between groups.

	Group								p'
	Garlic (n=40)				Placebo (n=40)				
	Before	After	Change	P	Before	After	Change	p	
TNF-α Serum	30,38± 2.61	17,9± 3,22	12,5± 3,46	0,000 ^a	22,46± 4,21	30,76± 2,45	-8,3±4,1	0,000 ^a	0,000 ^b

p: p-value before and after treatment. p': p-value after treatment between groups. a) Paired T-test b) Unpaired T-test, significant if $p < 0.05$.

Table 2 presents a comparison of TNF- α levels between groups. The results of the study showed that the administration of garlic extract was able to reduce TNF- α levels by 12.5 pg/mL, $p < 0.05$. In contrast, in the placebo group, there was an increase in TNF- α levels of 8.3 pg/mL, $p < 0.05$.

4. Discussion

The results of the study show that garlic extract has an effect and is effective in reducing serum TNF- α levels in chronic HD patients at Dr. Mohammad Hoesin General Hospital, Palembang, Indonesia. Induction of serum TNF- α production is influenced by systemic factors and local factors where macrophage activation by the inflammatory process in CKD will activate NF- κ B, which will release proinflammatory

cytokines, chemokines, and adhesion molecules, including TNF- α , ICAM 1, and MCP1. Whereas local hemodialysis factors such as the use of incompatible biofilters, double lumen catheters, and the influence of urea and endothelial disorders all of which will activate macrophages and endothelial cells, which in turn will activate NF- κ B that will produce proinflammatory cytokines, chemokines, and adhesion molecules, including TNF - α , ICAM 1 and MCP 1. Garlic has various bioactive compounds, including organosulfur compounds, saponins, phenolic compounds, and polysaccharides. The main active component of garlic is its organosulfur compound, namely γ -glutamyl-S-alk (en) yl-L-cysteine, which can be hydrolyzed and oxidized to produce S-alkyl (en) yl-L-cysteine sulfoxide (alliin).

Alliin is converted to allicin, which activates the alliinase enzyme. Allicin is very unstable and readily decomposes to form various volatile oil-soluble organosulfur compounds, which produce diallyl sulfide (DAS), diallyl disulfide (DADS), diallyl trisulfide (DATS), vinyl dithiin and ajoene. At the same time, γ -glutamyl -S-alk(en)yl-L-cysteine is also converted to water-soluble organosulfur compounds, including S-allyl cysteine (SAC) and S-allyl mercapto cysteine (SAMC).¹⁰⁻¹⁴

Oxidative stress, which is the precursor and product of inflammation, will stimulate the activation of signaling molecular mediators such as NF- κ B, which can increase the production of inflammatory cytokines. By administering garlic extract, the organosulfur compounds contained in garlic extract, such as S-allyl-cysteine (SAC), can prevent the activation of NF- κ B so that the induction of the production of proinflammatory cytokines such as TNF- α can be reduced. Reactive oxygen species (ROS), which is formed in the inflammatory process in CKD cases due to an increase in the amount of urea, will activate macrophages to release TNF- α . Allicin, which is the main active compound in garlic and also its derivative S-allyl-cysteine (SAC), which is an oxidizing agent, is reported to be able to inhibit ROS and inhibit pro-oxidant enzymes (nitric oxide synthase, xanthine, NADPH oxidase, and cyclooxygenase) as well as being able to induce antioxidant enzymes. Such as superoxide dismutase (SOD) and catalase (CAT), so that macrophage activation can be reduced and TNF- α production is also reduced. Alliin, which is also the main active component of garlic, is able to suppress LPS inflammatory signals by producing anti-inflammatory gene expression and preventing increased expression of the proinflammatory cytokine TNF- α . Giving garlic extract is able to inhibit the secretion of TNF- α . In addition to the organosulfur components, garlic also contains saponins which are powerful antioxidants, protecting cells by reducing ROS production in response to oxidative stress. Studies confirmed that garlic saponins function as antioxidants to protect rats' PC12 pheochromocytoma

cells from direct hypoxia-induced ROS damage and exert protective effects via ROS-mediated redox-sensitive signaling pathways. Another study found a role for SAMC in NF- κ B expression in kidney inflammation in cisplatin-induced rats. It was found that the activation of NF- κ B in the group given SAMC could be significantly inhibited compared to the group that did not receive SAMC.¹⁵⁻²⁰

5. Conclusion

Garlic extract (*Allium sativum*) is effective in reducing tumor necrosis factor- α (TNF- α) serum levels in chronic hemodialysis patients at Dr. Mohammad Hoesin Palembang Indonesia.

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