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COMPARISON OF THE EFFECT BAY LEAVES (SYZYGIUMPOLYANTHUM (WIGHT) WALP) WITH A DOSAGE OF 400MG AND 600MG TO HS-CRP IN PATIENTS WITH DYSLIPIDEMIA

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Abstract
Introduction: The use of herbal medicines has long been practiced throughout the world. The potential of the herbal medicine and phytopharmaca market in Indonesia is very large. **Aim:**to analyze the comparison of bay leaves with different doses of hs-CRP levels in dyslipidemic patients.
Method: This study is a prospective clinical trial design. Research will begin in August 2017 until February 2018 or until the number of research subjects is fulfilled. Provision and processing of test plants in collaboration with a team of pharmacists in the Laboratory of Traditional Medicine Section, Faculty of Pharmacy, University of North Sumatra. Analytical statistical analysis of the independent T Test or Mann Whitney U is used. Differences were considered statistically significant if the value of p <0.05.
Results : The subjects of the study amounted to 30 people divided into two groups, namely 15 subjects with a dose of 2x200 mg and 15 subjects with a dose of 2x300 mg. In the 2x200 mg dose group there was a significant decrease in mean hs-CRP before treatment compared to after treatment ((3.92 + 3.89vs2.34 + 2.22) mg / dL; p = 0.001; 95% CI). In the 2x300 mg group there was also a decrease in the mean hs-CRP before treatment compared with after treatment, but it was not statistically significant ((4.34 + 3.03 vs 3.45 + 2.88) mg / dL; p = 0.009; IK 95%). The mean reduction in hs-CRP in the 2x300 mg group compared with the 2x200 mg group was greater, statistically significant ((0.93 vs 1.58) mg / dL; p value = 0.005; 95% CI).
Conclusion: Giving salam leaf extract (Syzygiumpolyanthum (Wight) Walp) for 30 days there was a significant difference in the effect of giving bay leaves at different doses of 2x200mg vs. 2x300mg to hs-CRP levels in dyslipidemia patients.

Introduction
The use of herbal medicines has long been practiced throughout the world. It is estimated that 75 - 80% of people in developing countries and 25% in developed countries use traditional medicine as first-line treatment. Therefore, the production and processing of herbal medicines continues to be improved to treat various diseases. The potential market for herbal medicines and fitopharmaca in Indonesia is very large because Indonesia has more than 30,000 plant species and 940 of them are nutritious plants .[1]

Bay leaves contain tannin, galokatekin, flavonoids, saponins, and essential oils. Besides bay leaves also contain several vitamins, including vitamin A, vitamin C, vitamin E, thiamin, riboflavin, niacin, vitamin B6, vitamin B12, and folate. The results of in vitro studies show that flavonoids work as inhibitors of the HMG-CoA reductase enzyme so cholesterol synthesis decreases. Saponins can form complex insoluble bonds with cholesterol derived from food, bind to bile acids to form micelles and increase the binding of cholesterol by fiber so that cholesterol cannot be absorbed by the intestine. Tannin inhibits the absorption of fat in the intestine by reacting with mucous proteins and intestinal epithelial cells.[2,3]

The results of the study by Prahastuti et al. In dyslipidemia mice showed that the salam leaf infusion concentrated 5%, 10%, 20% for 2 weeks significantly reducing total cholesterol levels (p value <0.05). Salam leaves concentration of 5%, 10%, 20% has the same effect in reducing total blood cholesterol levels and its potential is equivalent to simvastatin.[2]

Siregar's research results on 20 people with hypercholesterolemia patients using a clinical test method without comparison showed that the combination of sambiloto and bay leaf extract with a dose of 3 x 1 capsule daily for 14 days significantly reduced cholesterol levels (p value <0.05) without side effects meaningful. The average reduction in cholesterol levels in 7 days was 55.80 + 16.30 mg / dL with a 95% confidence interval (95% CI). Decreasing cholesterol levels on day 7 was 20.03% and day 14 35.56%.[4]

Research by Tang et al. Reported that individuals suffering from dyslipidemia had high sensitive C reactive protein (hs-CRP), soluble intracellular adhesion molecule-1 (s-ICAM 1), and soluble E-selectin (sE-selectin) higher than those without dyslipidemia (p value <0.001). When compared with groups that have lower levels of inflammatory factors, patients with inflammatory factor levels in the highest quartile are more at risk of suffering from dyslipidemia (OR at 95% CI: 3,215 for hs-CRP, 1,575 for s-ICAM 1, and 1,495 for sE-selectin) In addition, only hs-CRP is associated with all components of dyslipidemia (p value <0.001), whereas s-ICAM 1 is not associated with HDL cholesterol or triglycerides, sE-selectin is only associated with triglycerides.[5]

So far no studies have analyzed the comparison of bay leaves with different doses of hs-CRP levels in dyslipidemic patients so the authors are interested in conducting this study.

Method

This study was a prospective clinical trial design where there were randomized and double-blinded treatment groups and control groups. The research will be conducted at the outpatient clinic at the Medan General Hospital RSUP with the approval of the USU FK Research Ethics Commission. Research will begin in August 2017 until February 2018 or until the number of research subjects is fulfilled.

The target population is all patients with dyslipidemia. Affordable population was all patients with dyslipidemia who were treated at the outpatient clinic at RSUP HAM Medan. Samples were dyslipidemic patients who were treated at the outpatient clinic at RSUP HAM Medan who met the study inclusion and exclusion criteria.

The inclusion criteria in this study were patients with dyslipidemia, age> 18 years, the subject gave informed consent. The exclusion criteria are taking antidyslipidemia drugs in the last 2 weeks, having impaired renal function, having liver function disorders, having other comorbidities such as DM, acute coronary syndrome (SKA), stroke, infectious disease, and impaired food intake due to gastrointestinal disease, and pregnant or currently in a pregnancy planning and breastfeeding program.

Provision and processing of test plants in collaboration with a team of pharmacists in the Laboratory of Traditional Medicine Section, Faculty of Pharmacy, University of North Sumatra. Making bay leaf extract is done by percolation. Then the pre-formulation test of the dry granule was carried out including the flow time test and the stationary angle determination. After that, an evaluation of the bay leaf capsule was evaluated according to what was stated in the 3rd edition of Pharmacopoeia Indonesia, including deviation of weight and disintegration time.

Descriptive statistical analysis is used for demographic data. Analytical statistical analysis of independent T test or Man Whitney U was used to examine differences in numerical variables between treatment and control groups. Dependent T test or Kolmogorof Semirnov to examine differences in numerical variables in each study group. Significant difference if the value of p <0.05.

Results

The subjects of the study amounted to 30 people divided into two groups, namely 15 subjects with a dose of 2x200 mg and 15 subjects with a dose of 2x300 mg. The characteristics of the research subject are explained in table 1.

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Table 1. Subject Characteristic

Characteristic	Group A 2x200 (n = 15)	Group B 2x300 (n = 15)	P
Sex Female/Male	15 / 0	14/ 1	-
Age(year)	50.40 ±5.22	50.07 ±4.73	0.818
AC (cm)	88,33 ± 7,18	92,36 ± 8,54	0.207
Height (m)	1,56 ±0.04	1,55±0,05	0.932
Weight(kg)	67.00 ±10.65	66.33±5.56	0.787
BMI(kg/m^2)	27.54 ±3.22	27.40±0.97	0.836
SBP (mmHg)	118,33 ± 5,23	118,67 ± 7,19	0.928
DBP (mmHg)	77,33 ± 4,58	76,00 ± 5,07	0.446
KT (mg/dL)	229,13 ± 14,99	271,73 ± 52,17	0.005*
LDL (mg/dL)	155,00 ± 22,55	175,73 ± 35,40	0.066
HDL (mg/dL)	51,13 ± 7,73	49,33 ± 8,53	0.550
TG (mg/dL)	149,93 ± 70,56	202,80 ± 114,57	0.139
Hs-CRP	3,92 ± 3,89	4,38 ± 3,03	0.009*
FBG (mg/dL)	94,20 ± 15,03	91,47 ± 85,00	0.604
Ureum (mg/dL)	21.93 ±10.35	25.13±13.75	0.244
Creatinin (mg/dL)	0.61±0.10	0,75 ± 0,28	0.271

*Significant

Comparisons between hs-CRP levels and group lipid profiles in doses of 2x200mg and 2x300mg groups are presented in Table 2.

Table 2. Comparison of hs-CRP levels and group lipid profiles in doses of 2x200mg (A) and groups of 2x300mg (B)

Variable	Group A (n = 15) Mean ± SD				Group B(n = 15) Mean ± SD				Δ*p*
	H_0	H_{30}	Δ	p_a	H_0	H_{30}	Δ	p_b	
Hs-CRP	3,92± 3,89	2,34± 2,22	1,58	0,001	4,34± 3,03	3,45± 2,88	0,93	0,009	0,005
KT (mg/dL)	229,13 ± 14,99	217,53 ± 23,10	11,60	0,012	271,73 ± 52,17	225,93 ± 30,80	45,80	**0,002**	0,785
LDL (mg/dL)	155,00 ± 22,55	145,67 ± 29,37	9,33	0,035	175,73± 35,40	145,72± 33,10	30,47	**0,001**	0,573
HDL (mg/dL)	51,13 ± 7,73	50,07 ± 7,5	1,07	**0,318**	49,33 ± 8,53	47,73 ± 5,80	1,60	0,344	**0,935**
TG (mg/dL)	149,93 ± 70,56	112,13 ± 37,92	37,80	0,009	202,80 ± 114,57	138,60 ± 49,76	64,2	0,016	0,050

Discussion

CRP is an acute phase protein, a non-specific systemic inflammatory marker. Its level increases in response to infections, inflames and tissue damage. CRP is normally found in human serum but in very small amounts and levels differ in each individual. In healthy individuals without inflammation, usually CRP levels <1 mg / L with median 0.8 mg / L.

When inflammation, infection and tissue damage occur, CRP is synthesized and secreted by the liver in response to cytokines, especially interleukin-6 (IL-6), interleukin-1 (IL-1), and TumorNecrosis Factor (TNF) -α produced by macrophages. CRP levels also increase in hypertension, diabetes, dyslipidemia, smoking and a history of heart disease.[6]

Unlike CRP, hs-CRP is an examination that can measure very little CRP concentration so that it is more sensitive with a measurement range between 0.1 - 20 mg / L. hs-CRP is good for examining the existence of a low level inflammation such as atherosclerosis.[7,8]

The relationship of hs-CRP to the risk of cardiovascular disease has been reported by various studies. The research women's health study (WHS), reported that hs-CRP is a stronger predictor of cardiovascular events than LDL cholesterol.[8]

In this study it was found that there was a statistically significant difference in hs-CRP reduction in the 2x300 mg group compared to the larger 2x200 mg group ((0.93 vs 1.58) mg / dL; p = 0.005; 95% CI). The results of this study indicate the results of previous studies, namely Tang et al. Reported that individuals suffering from dyslipidemia had high sensitive C reactive protein (hs-CRP), soluble intracellular adhesion molecule-1 (s-ICAM 1), and soluble E-selectin (sE-selectin) is higher than those without dyslipidemia (p value <0.001). Inflammatory factors in the highest quartile are more at risk of developing dyslipidemia (OR at 95% IK: 3,215 for hs-CRP, 1,575 for ICAM 1, and 1,495 for sE-selectin). In addition, only hs-CRP is associated with all components of dyslipidemia (p value <0.001), whereas s-ICAM 1 is not associated with HDL cholesterol or triglycerides, sE-selectin is only associated with triglycerides.[5]

The inflammatory process that plays a role in this matter can be explained by the release of various local mast cell mediators such as histamine and bradykinin. This event is accompanied by activation of complement, coagulation system, inflammatory cells and endothelial cells which each release mediators which cause systemic effects such as heat , neutrophilia and acute phase protein production. One of the acute phase proteins is CRP. Increased CRP synthesis will increase plasma viscosity so that the erythrocyte sedimentation rate will also increase so the migration of inflammatory cells (macrophages, T lymphocytes) to the arterial wall is very closely related to vascular changes leading to atherosclerosis.[9]

Dyslipidemia has been confirmed as a risk factor for atherosclerosis and cardiovascular disease. Meanwhile, atherosclerosis is widely known as a vascular disease due to chronic inflammation and is the single most important contributor to cardiovascular disease. Clinical and epidemiological studies have shown that inflammatory factors are associated with atherosclerosis, which causes myocardial infarction and stroke. Inflammation is triggered by the entry of lipoprotein-rich cholesterol into the walls of blood vessels and is followed by macrophages and ultimately foamcells are formed.[5]

Yudkin et al. in diabetic patients it shows that increased CRP levels are strongly associated with components of the insulin resistance syndrome. Another study in 37 hypercholesterolemic patients and 37 controls showed that there was a significant relationship between hs-CRP with total cholesterol, LDL, oxidized LDL, oxidized LDL autoantibodies, HDL, and triglycerides.[5]

The results of this study showed that there were significant differences in total cholesterol, LDL cholesterol, and triglyceride levels with a p value of <0.05 before administration with after giving bay leaves at each different dose. The results of this study also showed similar results with previous studies, namely by Choudry et al.

showed that hs-CRP had a positive relationship with total cholesterol (p value = 0,0001), triglycerides (p value = 0,023), and LDL cholesterol (p value = 0,14).

Siregar also reported the results of 20 people with hypercholesterolemic patients using a clinical trial method without comparison showing that the combination of sambiloto and bay leaf extract with a dose of 3 x 1 capsule daily for 14 days significantly reduced cholesterol levels (p value <0.05) without side effects meaningful. The average reduction in cholesterol levels in 7 days was 55.80 + 16.30 mg / dL with a 95% confidence interval (95% CI). Decreasing cholesterol levels on day 7 was 20.03% and day 14 35.56%.[4]

Research Vienna Yulinda et al. Combination of sambiloto extract (Andrographis paniculata) and bay leaf(Syzygiumpolyanthum (Wight) Walp) 2 x @ 150 mg for 30 days in 15 patients with dysipidemia compared with Simvastatin 1x20 mg for 30 days in 15 patients with dysipidemia found to reduce levels of hs-CRP and lipids the profile is greater in the combination of bitter (Andrographis paniculata) and bay leaves (Syzygiumpolyanthum (Wight) Walp)than simvastatin 1 x 20 mg.[10]

Although the results of this study showed that there were significant differences between the levels of total cholesterol, LDL, HDL, and TG before and after administration of bay leaves in each dose, when compared to the dose of 2x200 mg with 2x300 mg did not show differences in total cholesterol, LDL, HDL, and significant TG.

Conclusion

The conclusion is that 30 days of bay leaf extract (Syzygiumpolyanthum (Wight) Walp) was given a significant difference in the effect of giving bay leaves at different doses of 2x200mg vs. 2x300mg to hs-CRP levels in dyslipidemia patients and found a significant difference in the effects of different bay leaves dosage of triglyceride levels in dyslipidemic patients.

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