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COMPARISON THE EFFECT OF COMBINATION SAMBILOTO EXTRACT *(ANDROGRAPHIS PANICULATA (BURM.F.) NEES)* AND SALAM *(SYZYGIUM POLYANTHUM (WIGHT) WALP)* WITH SIMVASTATIN ON APO-B CONCENTRATION IN DYSLIPIDEMIA PA

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ABSTRACT

Background : Dyslipidemia is risk factor of cardiovascular disease and significantly correlated with increased Apo-B concentration. Simvastatin, a sintetic antidyslipidemic drug,can decreaseApo-B concentration. But long term use of sintetic drug may cause side effects, so that phytopharmaca is begin to reuse. Combination sambiloto extract and salam could decrease cholesterol, triglyceride, and proinflammatory cytokines. Aim of this study was to compare the effect of combination sambiloto extract and salam with simvastatin onApo-B concentration in dyslipidemic patients. **Method :** This clinical trial use prospective design. Study group (n = 15) and control group (n = 15) were choosen with double blind random sampling. Before and after 30 days theraphy, blood sample was taken. Data was analysed with SPSS, if p< 0.05 was considered significant difference. **Result:** Before and after 30 days theraphy was there was insignificant increase of Apo-B in study group(106,93 + 17,56 VS 107,73 + 26,96) mg/dL; p = 0,463); meanwhile significant decrease was there in control group(117,46 + 27,13 vs 101,80 + 30,01) mg/dL; p = 0,001). Apo-B decrease of control group was biger than that of study group, but statistically insignificant (-0,80 + 33,42 vs 15,66 + 16,85) mg/dL; p = 0,0125).**Conclusion:** Combination sambiloto extract (Andrographis paniculata) and salam (Syzygium polyanthum)2 x @ 150 mg for 30 days not decreased Apo-B concentration than simvastatin 1 x 20 mg, with statistically insignificant.

KEYWORDS : Apo-B, Andrographis paniculata and Syzygium polyanthum, dyslipidemia

1. INTRODUCTION

Dyslipidemia is a risk factor for cardiovascular disease and is significantly associated with increased levels of Apo-B. 1,2,3,4,5 Simvastatin, a synthetic antidislipidemia drug, can reduce Apo-B levels. 6,10,11,24 However, the use of long-term synthetic drugs can cause side effects so that phytopharmaca begins to be reused.5 Many phytopharmaca have proven effective in improving metabolic function, one of which is dhawalsan-1 (Curanga fel-terrae), whose potential is equivalent to metformin in new type 2 DM patients.[7]

Previous research reported that a combination of bitter extract and bay leaves reduced cholesterol levels better than a single. Sambiloto has extensive pharmacological effects such as anti-inflammatory, antidislipidemia, cardioprotective, etc.8 Infusion of bay leaves concentrations of 5%, 10%, 20% significantly reduce total cholesterol levels (p <0.05) in dyslipidemic mice, and the potential is equivalent to simvastatin. 9 Preclinical studies in rats showed that the combination of bitter extract and bay leaves lower cholesterol levels stronger than single sambiloto extract or single bay leaf; and the effect of this combination is equivalent to gemfibrozil.8 The results of Siregar's research on 20 people with hypercholesterolemia showed that the combination of sambiloto extract and bay leaves with a dose of 3 x1 capsules (containing 100 mg of sambiloto extract and 100 mg of bay leaf extract) for 14 days significantly decreased levels of cholesterol (p <0.05) without significant side effects.[4]

This study aims to compare the effects of the combination of bitter extract and bay leaves with simvastatin on Apo-B levels in dyslipidemic patients.

2. METHOD

This clinical trial research with prospective design was carried out at Haji Adam Malik General Hospital Medan from January to December 2016 with the approval of the USU FK Research Ethics Committee / Medan HAM Hospital. Based on NCEP / ATP III dyslipidemia is a metabolic disorder of one / more lipoproteins (an increase in total cholesterol> 240 mg / dL or LDL> 160 mg / dL or triglycerides> 200 mg / dL, or a decrease in HDL <40 mg / dL) .12 Dyslipidemia patients those aged> 18 years and willing to take the written study; without a history of taking antidyslipidemia drugs last 2 weeks, impaired liver or kidney function, there are other comorbidities (diabetes mellitus, acute coronary syndrome, stroke, infectious diseases, intake disorders), pregnant / breastfeeding recruited to take part in the study.

Sambiloto extract and bay leaves are made by the USU Pharmacy Department with percolation techniques. A total of 150 mg of sambiloto extract and 150 mg of bay leaf extract were put into capsules and added to lactose to a total weight of 500 mg / capsule. To disguise this type of drug, simvastatin 20 mg was also put into a similar capsule and added to lactose to a total weight of 500 mg / capsule. The treatment group (n = 15, given a combination of bitter extract and bay leaf 2 x @ 150 mg) and the control group (n = 15, given simvastatin 1 x 20 mg) were randomly selected randomly, and kept secret until data analysis was complete. Before and after 30 days of treatment, anthropometry, blood pressure and blood samples were examined.

Data were analyzed by SPSS. The Shapiro-Wilk test was conducted, if the data were normally distributed then analyzed by chi square test, paired T test, or unpaired T test. If the data is not normally distributed then it is analyzed by testing Fishers' exact, Wilcoxon test, or Mann-Whitney U test. Significant difference if the value of p <0.05.12.13

3. RESULT

Before being given the drug, there were no significant differences in the characteristics of the treatment subjects and the control group. The initial urea level of the treatment group and control group was still in the normal range.

Table 1. Basic characteristic of research subject

Basic Characteristic	Study Group (n = 15)	Control Group (n = 15)	p
Sex Woman / Man	11 / 4	8 / 7	0.225
Age(tahun)	54.80 + 13.04	47.47 + 11.50	0.057
WS (cm)	88.33 + 7.18	92.36 + 8.54	0.095
Weight(kg)	63.97 + 11.23	65.62 + 10.77	0.342
IMT(kg/m2)	26.19 + 4.42	26.02 + 3.37	0.452
SBP (mmHg)	136 + 31.12	125.33 + 13.02	0.328
DBP (mmHg)	78.66 + 13.02	83.33 + 15.43	0.220
Apo-B (mg/L)	3.02 + 3.13	2.78 + 1.97	0.302
Leukocyte(/µL)	7308 + 1729	7518 + 1488	0.362
BSR (mm/jam)	27.73 + 19.37	26.93 + 21.23	0.458
TC (mg/dL)	234 + 29.21	233.66 + 49.52	0.491
LDL (mg/dL)	160.53 + 30.97	159.66 + 41.91	0.354
HDL (mg/dL)	45.13 + 8.01	43.33 + 12.59	0.332
TG (mg/dL)	158.20 + 147.47	159.86 + 72.85	0.127
FBG (mg/dL)	82.20 + 13.67	85.33 + 9.74	0.131
SGOT (U/L)	19.93 + 5.88	23.13 + 7.02	0.093
SGPT (U/L)	19.86 + 11.66	24.80 + 12.54	0.118
Ureum (mg/dL)	17.86 + 5.47	18.33 + 6.45	0.369
Creatinine (mg/dL)	0.71 + 0.18	0.83 + 0.17	0.035*

The Each study subject was examined for Apo-B levels, inflammatory markers, and lipid profiles before and after treatment as detailed in table 2.

Table 2. Comparison of Apo-B levels, inflammatory markers, and lipid profiles and control groups

Variable	Study Group (n = 15) Mean + SD				Control Group (n = 15) Mean + SD				p delta
	H0	H30	delta	pa	H0	H30	delta	pb	
Apo-B (mg/dL)	106,93+ 17,56	107,73+ 26,96	-0,80+ 33,42	0,463	117,46+ 27,13	101.80+ 30,01	15,66+ 16,85	0,001*	0.0125*
Leukocyte (/µL)	7308 + 1729	6893 + 1222	533+ 1311	0.094	7518 1488	7378 1498	140 + 1329	0.213	0.346
Neutrophils(%)	56.46 + 10.50	52.04 + 7.59	4.42 + 7.72	0.022 *	54.12 + 7.83	57.42 + 6.35	-3.30 + 5.08	0.012*	0.001 *
Lymphocy (%)	31.31 + 9.28	35.54 + 7.42	-4.23 + 5.46	0.005 *	34.18 + 6.67	30.79 + 4.86	3.39 + 4.71	0.007*	0.000 *
BSR (mm/jam)	27.73 + 19.37	24.66 + 17.24	3.06 + 11.00	0.149	26.93 + 21.23	23.26	3.66 + 13.52	0.264	0.369
TC (mg/dL)	234 + 29.21	210 + 50.45	23.86 + 57.08	0.064	233.66 + 49.52	200 + 56.15	33.40	0.000*	0.289
LDL (mg/dL)	160.53 + 30.97	145.46 + 47.97	15.06 + 40.15	0.105	159.66+ 41.91	131.93 + 47.72	27.73	0.002*	0.171
HDL (mg/dL)	45.13 + 8.01	38.46 + 8.26	6.66 + 5.55	0.000 *	43.33 + 12.59	42.33	1.00 + 8.15	0.181	0.017 *
TG (mg/dL)	158.2 + 147.67	150.46 + 94.79	7.73 + 72.38	0.294	159.86 + 72.85	152.80 + 71.02	7.06 + 71.48	0.477	0.442

The results of this study showed that before treatment compared with after treatment there was a no significant decrease in Apo-B levels ((106,93 + 17,56 vs 107,73 + 26,96) mg / dL; p = 0.463) in the treatment group and significant reduction ((117,46 + 27,13 vs 101,80 + 30,01) mg / dL; p = 0.001) in the control group. The decrease in Apo-B levels in the control group was greater than the treatment group, andwasstatistically significant ((15,66 + 16,85 vs -0,80 + 33,42) mg / dL; p = 0.0125).

There have been no previous studies that have studied the effects of combination of bitter extract (Andrographis paniculata) and bay leaf (Syzygium polyanthum) on Apo-B levels in dyslipidemic patients.

4. DISCUSSION

The results of this study showed that before treatment compared with after treatment there wasn't a significant reduction in APO-B levels (106,93 + 17,56 VS 107,73 + 26,96) mg/dL; p = 0,463) in the treatment and significant decrease (117,46 + 27,13 vs 101,80 + 30,01) mg/dL; p = 0,001) in the control group. The decrease in APO-B levels in the control group was greater than the treatment group, and statistically significant (-0,80 + 33,42 vs 15,66 + 16,85) mg/dL; p = 0,0125).

There have been no previous studies that studied the effect of the combination of bitter (Andrographis paniculata) and bay (Syzygium polyanthum) extracts on APO-B levels in dyslipidemic patients. Andrographis paniculata contains several active substances, including andrographolide, deoxyandrographolide, neoandrographolide, flavonoids, tannins, saponins that can inhibit the inflammatory process and reduce cholesterol and triglyceride levels. 21,22,23Bay leaves can reduce serum LDL cholesterol levels significantly according to the increase in dosage given because salads contain active compounds such as quercetin contained in flavonoids besides their properties as antioxidants, can inhibit secretions from Apo-B100 to the intestine, so the number of Apo B will decrease. Apo-B is a form of VLDL and LDL. Based on a survey of 40,000 adult women in the United States, it was found that women who consumed foods with flavonoid content, 35% of them were free from cardiovascular disease. The high content of quercetin in a food can modulate the activity of platelets to prevent cardiovascular disease.[24]

The results of this study showed that before treatment compared with after treatment there was a significant decrease in neutrophil counts ((56.46 + 10.50 vs 52.04 +7.59)%; p = 0.022) in the treatment group and a significant increase ((54.12 + 7.83 vs. 57.42 +6.35)%; p value = 0.012) in the control group. The decrease in neutrophil count in the treatment group was significantly greater than the control group ((4.42 + 7.72 vs-3.30 + 5.08)%; p = 0.001). In addition, before treatment compared to after treatment there was a significant increase in lymphocyte counts ((31.31 + 9.28 vs 35.54 + 7.42)%; p = 0.005) in the treatment group and a significant decrease ((34.18 + 6.67 vs. 30.79 + 4.86)%; p = 0.007) in the control group. Increased lymphocyte count in the treatment group was significantly greater than the control group ((-4.23 + 5.46 vs 3.39 + 4.71)%; p = 0.000).

There have been no previous studies that studied the effect of giving a combination of bitter and bay leaf extracts to neutrophils and lymphocytes. However, previous studies reported that methanol extract of Andrographis paniculata inhibited the formation of ROS invitro and completely inhibited carrgeenan-induced inflammation. Inhibition of ROS production is partly mediated by PKC activation by PMA and partly mediated by down-regulation of surface expression of Mac-1 (essential integrins for adhesion and neutrophil transmigration) .14,15 Other studies report that andrographolide weakens TNAM-1 expression induced by TNF -α (the main pathway of the inflammatory process) and through inhibition of neutrophil transmigration.21 Thus Andrographis paniculata extract can reduce the neutrophil count of dyslipidemia patients as reported in this study. Another study reported in vitro lymphocyte incubation with 1 micromolar andrographolide increasing the number of CD3 lymphocytes (61 - 91%), CD4 (40 - 61%) and CD56 (2 - 3%) compared with control lymphocytes.[20]

The results of this study indicate that before treatment compared to after treatment there was a significant reduction in the number of leukocytes ((7308 + 1729 vs 6893 + 1222) / µL; p = 0.094) in the treatment and control groups ((7518 + 1488 vs 7378 + 1498) / µL; p = 0.213). The decrease in the number of leukocytes in the treatment group was greater than in the control group, but not statistically significant ((533 + 0.13 vs 140 + 1329) / µL; p = 0.346). In addition, before treatment compared to after treatment, there was a non-significant decrease in LEDs ((27.73 + 19.37 vs 24.66 + 17.24) mm / hour; p = 0.149) in the treatment and control groups ((26.93 + 21.23 vs 23.26 + 18.19) mm / jam; p = 0.264). The decrease in LED in the treatment group was smaller than the control group, but it was not statistically significant ((3.06 + 11.00 vs. 3.66 + 13.52) mm / hour; p = 0.369).

This research is in line with the research of Agarwal et al. who reported that the administration of Andrographis paniculata 600 mg per day (increased dose to a maximum of 1.8 g per day according to tolerance) in type 2 DM patients did not cause significant changes in leukocyte or LED counts after 12 weeks consuming Andrographis paniculata capsules.[22]

The results of this study showed that the combination of bitter (Andrographis paniculata) and bay leaves (Syzygium polyanthum) with a dose of 2 x 1 capsule (containing 150 mg of bitter extract and 150 mg of bay leaf) for 30 days did not cause significant side effects on liver function and kidney function, as well as giving simvastatin 1 x 20 mg for 1 month.

The weakness of this study is that even though the research subjects have been given education about the recommended diet in dyslipidemia, food menu and physical activity are not uniformized in the research subject so that it can cause bias in the results of the study. Research time (30 days) is too short to detect long-term side effects that may arise due to the combination of bitter (Andrographis paniculata) extract and bay leaf (Syzygium polyanthum).

5. CONCLUSION

I The combination of bitter extract (Andrographis paniculata) and bay leaves (Syzygium polyanthum) 2 x @ 150 mg for 30 days was not reduced APO-B levels greater than simvastatin 1 x 20 mg, and was not statistically significant (p> 0.05).

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