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Comparison of sambiloto (*Andrographis paniculata* (Burm.f.) Nees) and Salam (*Syzygium polyanthum* (wight) walp) extract mixture with simvastatin on ferritin concentration in dyslipidemic patients

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Abstract
Background: Dyslipidemia is one of many risk factor in cardiovascular diseases and significantly correlated with increased inflammation marker, including ferritin concentration. Synthetic antidyslipidemic drugs, such as Simvastatin, may decrease ferritin concentration, even without many supporting study. However, long term use of synthetic drugs could cause side effects, so that phytopharmaca is becoming to consideration. The mixture of sambiloto and Salam extracts reported decreasing proinflammatory cytokines, cholesterol, and triglyceride. We try to compare the effect of sambiloto and Salam extract mixture with simvastatin on Ferritin concentration in dyslipidemic patients in this study.
Method: This clinical trial use prospective design with double blinded random sampling that involved 30 patients divided by two groups (simvastatin and sambiloto and Salam extract mixture).
Result: Ferritin concentration before therapy compared to after examination was decreased but it was statistically insignificant ((150, 09 + 104, 95 vs 133, 63 + 94, 77) ng/dL; p = 0,079) not only in study group but also in control group ((172, 44 + 162, 7 vs 160, 75 + 164,7) ng/dL; p = 0,325). The decrease of ferritin in study group was bigger than the control group, but it was statistically insignificant ((17, 2 + 45,24 vs 11,69 + 53,15) ng/dL; p = 0,221).
Conclusion: The mixture of sambiloto (*Andrographis paniculata*) and Salam (*Syzygium polyanthum*) extract decreased ferritin concentration bigger than simvastatin, but statistically insignificant.

Keywords: Ferritin, *Andrographis paniculata* and *Syzygium polyanthum*, dyslipidemia

1. Introduction
Dyslipidemia is a very important risk factor in cardiovascular diseases that has become number one cause of death in the world. In 2013, the prevalence of vascular disorder such as stroke has already been as high as 17, 9% in Sumatera Province, Indonesia. Dyslipidemia has been known to contribute in inflammation process and there are some markers that increased, such as C - reactive protein (CRP), Inter-leukin 1 (IL-1), IL6 and many more. Until now, statins, even though reported have some side effects in long term use, are known as the standard medication for the dyslipidemic patients. Nowadays, there has been a new trials to use herbs as an alternative to these standard drugs with minimal side effects, especially sambiloto and Salam [1, 8].
Previous study reported that the mixture of sambiloto and Salam extract reduced cholesterol more than single usage of the herbs. Sambiloto has a broad pharmacology effect, such as anti-inflammation, anti-dyslipidemia, cardio protective, etc. Concentration of 5%, 10%, and 20% shows significant decreased of total cholesterol (p<0.05) in dyslipidemic rats, and its potential is same as simvastatin [9, 10]. Pre-clinical study in rats showed that the mixture of sambiloto and Salam extract reduced cholesterol stronger than single sambiloto or Salam extracts and this combination effects is on par with gemfibrozil [11]. A study by Siregar in 20 patients with hypercholesterolemia showed a significant decreased of total cholesterol using the herbs extract in 14 days [5].

2. Method
This study is a clinical trial with a double blinded prospective study conducted in Haji Adam

Malik Hospital Medan, Indonesia from January 2016 until December 2016 with a local ethical committee approval. The inclusion criteria in this study were male and female patients aged over 18 years and willing to participate in the study; no history of taking anti-dyslipidemic drugs for 2 weeks prior; no history of liver and kidney diseases; no history of diabetes, cardiovascular disease, infectious diseases, gastrointestinal problems and pregnant or breastfeeding woman.

The sambiloto and Salam extracts were produced by the pharmaceutical department Universitas Sumatera Utara, Medan, Indonesia. As much as 150 mg of sambiloto and Salam extract inserted to a capsule and added lactose until 500 mg per capsule. We also inserted the simvastation 20 mg to the capsule. The study group (n= 15) were given the mixture of the extracts and the control group (n= 15) were given the simvastatin and chosen randomly double blinded until data analysis has been done. Before and after 30 days of therapy, we check the anthropometry, blood pressure and the laboratories sample.

Data analyzed with SPSS. We conducted Shapiro-Wilk test, if the data distributed normally and then analyzed them with *chi square test*, paired T-test or unpaired T-test. If the data then distributed abnormal, we analyzed them with *Fishers' exact,* Wilcoxon test, or Mann-Whitney U test. It's significant if the $p < 0.05$ [13].

3. Result

Before given drugs, there were no significant difference in both the study group and control group. (Table 1)

Table 1: Baseline Characteristics of the Subject

Parameter	Study Group (n = 15)	Control Group (n = 15)	p
Gender Female / Male	11 / 4	8 / 7	0,225
Age (years)	54,80 + 13,04	47,47 + 11,50	0,057
AC (cm)	88,33 + 7,18	92,36 + 8,54	0,095
Weight (kg)	63,97 + 11,23	65,62 + 10,77	0,342
BMI (kg/m^2)	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
Eritrocyte	4706 + 444	4826 + 400	0,229
Hemoglobin	13,46 + 1,30	14,37 + 1,46	0,042*
RDW	13,62 + 1,17	13,16 + 0,92	0,095
Ferritin (mg/L)	150,93 + 104,95	172,44 + 162,70	0,458
Leukocyte (/µL)	7308 + 1729	7518 + 1488	0,362
Neutrophyl (%)	56,46 + 10,50	54,12 + 7,83	0,247
Limphocyte (%)	31,31 + 9,28	34,18 + 6,67	0,169
ESR (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*

Description: AC: Abdominal Circumference, BMI: Body Mass Index, SBP: Systolic Blood Pressure, DBP: Diastolic Blood Pressure, ESR: Estimated Sedimentation Rate, TC: Total Cholesterol, LDL: *Low Density Lipoprotein*, HDL: *High Density Lipoprotein*, TG: Triglyserida, FBG: Fasting Blood Glucose, SGOT: *Serum Glutamic Oxaloacetic Transaminase*, SGPT: *Serum Glutamate Pyruvate Transaminase*, *: significant.

We had ferritin, inflammation marker and lipid profile examinations before and after given treatment on each and every subjects. (Table 2)

Table 2: Comparison of Ferritin levels, inflammatory markers, and lipid profiles in Control and Study Groups

Variables	Study Group (n = 15) Mean + SD				Control Group (n = 15) Mean + SD				Δ*p*
	H_0	H_{30}	Δ	p_a	H_0	H_{30}	Δ	p_b	
Feritin	150,9 + 104,95	133,63 + 94,77	17,20 + 45,24	0,079	172,44 + 162,70	160,75 + 164,70	11,69 + 53,15	0,325	0,221
Leucocyte (/µL)	7308 + 1729	6893 + 1222	533 + 1311	0,094	7518 + 1488	7378 + 1498	140 + 1329	0,213	0,346
Neutrophyl (%)	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*
Limphocyte(%)	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*
ESR (mm/hr)	27,73 + 19,37	24,66 + 17,24	3,06 + 11,00	0,149	26,93 + 21,23	23,26 + 18,19	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 + 32,63	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 + 15,06	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 + 12,86	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

Description: ESR: Estimated Sedimentation Rate, TC: Total Cholesterol, LDL: *Low Density Lipoprotein*, HDL: *High Density Lipoprotein*, TG: Triglyserida,
*: significant.

The results of this study showed that the comparison before and after treatment, there was no significant decreased of ferritin levels ((150.9 + 104, 95 vs 133.63 + 94.77) ng / dL; p = 0.079) both in the study group and control group ((172.44 +

162.70 vs 160.75 + 164.70) ng / dL; p = 0.325). The decrease in ferritin levels in the study group was greater than the control group, but statistically insignificant ((17, 20 + 45, 24 vs 11, 69 + 53, 15) ng / dL; p = 0.0221).

There have been no previous studies that have studied the effects of the mixture of sambiloto (Andrographis paniculata) and Salam (Syzygium polyanthum) extracts on ferritin levels in dyslipidemic patients.

There were 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 decreased in the number of leukocytes in the study group were 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 ESRs ((27.73 ± 19.37 vs 24.66 ± 17.24) mm / hour; p = 0.149) in the study and control groups ((26.93 ± 21.23 vs 23.26 ± 18.19) mm / jam; p = 0.264). The decreased in ESR 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).

There were a significant decreased in neutrophil counts ((56.46 ± 10.50 vs 52.04 ± 7.59)%; p = 0.022) in the study group and a significant increase ((54.12 ± 7.83 vs. 57.42 ± 6.35)%; p value = 0.012) in the control group. The decreased 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).

4. Discussion

There have been no previous studies that studied the effect of giving a combination of sambiloto and Salam extracts to ferritin in dyslipidemic patients. Studies from Sivasankari, Yamada, Ellidag shows that there was a significant increase of ferritin in metabolic syndrome patient compare to control [14, 16]. In this study, we can see the decreased of ferritin before and after treatment both in study and control group even though it's statistically insignificant (p= 0.079; p= 0.221). This study is similar to Yoon, *et al* which concluded that ferritin in statin group is lower than in control group after 30 days. The median of ferritin in statin group after treatment is 161.0 ng/dl,while in control group is 166.1 ng/dl. However, it's not statistically significant (p> 0.05) [17].

Another study from Ukine, *et al* shows different results from this study. The study shows a significant decrease of ferritin before and after given simvastatin and atorvastatin, especially in Type 2 Diabetes Mellitus patients (p<0.0001). There was a positive correlation between ferritin and LDL, and negative correlation with HDL (p=0.028; p=0.043) [18].

There have been no previous studies that studied the effect of giving a combination of sambiloto and Salam extracts to neutrophils and lymphocytes. However, previous studies reported that methanol extract of Andrographis paniculata inhibited the formation of ROS *in vitro* 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) [15, 16]. 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.[17] 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 lymphocytesn [19].

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 [20].

The results of this study showed that the combination of sambiloto (Andrographis paniculata) and Salam (Syzygium polyanthum) with a dose of 2 x 1 capsule (containing 150 mg of sambiloto and 150 mg of Salam extract) 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 uniformed 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 sambiloto (Andrographis paniculata) and Salam extract (Syzygium polyanthum).

5. Conclusion

The mixture of sambiloto (*Andrographis paniculata*) and Salam (*Syzygium polyanthum*) extract decreased ferritin concentration bigger than simvastatin, but statistically insignificant.

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