International Journal of Science and Research (IJSR)
ISSN: 2319-7064
ResearchGate Impact Factor (2018): 0.28 | SJIF (2019): 7.583

Clinical Trial of Herbal Products Combination of Extract *Gynura procumbens* Leaves and *Curcuma xanthorrhiza* Rhizome as Anti-dyslipidemia

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Abstract: ***Various risk factors are involved in the incidence of cardiovascular disease, one of which is dyslipidemia. The objective of this study is to determine the safety and efficacy of herbal product. This study used pre and post controlled group design, randomized controlled trial and open label by employing 50 subjects. The subjects were divided into 2 groups, i.e. simvastatin and herbal product. Group I received simvastatin with dose of 10 mg/day and group II received herbal product with dose of 3x10mL for 30 days. The efficacy of herbal product was evaluated with the ability to decrease total cholesterol, triglycerides, LDL, and increase HDL. The safety was evaluated with hematology, blood chemistry, and vital sign examinations performed before and after treatment. Data were analyzed using chi-square, paired T-test, independent T-test, Wilcoxon, and Mann-Whitney with a confidence level of 95% (P <0.05). The simvastatin group shows significant results (P<0.05) in decrease total cholesterol and LDL. The herbal group shows significant results (P <0.05) in decreasing triglycerides, however, there was no effect on total cholesterol and LDL. Simvastatin and herbal product have the same efficacy (P>0.05) in increasing HDL. Simvastatin and herbal product show no adverse effect based on laboratory and clinical assay.***

Keywords: Clinical trial**,** *Gynura procumbens*, *Curcuma xanthorrhiza*, Dyslipidemia

1. Introduction

Dyslipidemia increases the incidence of coronary heart disease with manifestations of thrombus and plaque in coronary arteries. In 2008 an estimated 17.3 million deaths were caused by cardiovascular disease. More than 3 million deaths occurred before the age of 60 years and were preventable. Some risk factors for cardiovascular disease were hypertension, diabetes mellitus, dyslipidemia, lack of physical activity, unhealthy diet, and stress [1]. In Indonesia people tend to follow a lifestyle of convenience including not exercising and consuming fast food. It can cause an increase in the number of people who experience dyslipidemia. High-fat diets have been shown to increase triglyceride levels in the blood [2]. Dyslipidemia is characterized by the increases and decreases in lipid fraction in plasma, especially an increase in total cholesterol, low density lipoprotein (LDL), triglycerides, and decrease of high density lipoprotein (HDL) levels [3].

Some synthetic drugs are effective in reducing total cholesterol, LDL, triglycerides, and increasing HDL. However, they have serious side effects are they used continuously. The FDA reported the need for caution in using statin drugs related to reports of side effects such as impaired liver function, memory disorders, increased blood sugar levels for people with diabetes mellitus, and muscle disorders [4]. Accordingly, safe and natural ingredients are needed for the treatment of dyslipidemia. Indonesian people often use the natural materials around them, including *Gynura procumbens* (Lour.) Merr. *(G. procumbens)* leaves and *Curcuma xanthorrhiza* Roxb. (*C. xanthorrhiza*) rhizome which have been used empirically to reduce cholesterol and lipid levels [5] and [6].

In this present study, the combination of *C. xanthorrhiza* rhizome extract and *G. procumbens* leaves extract in a ratio of 1:4 was made into herbal products formulated in syrup form in sachet packages containing 10 mL. The results of preclinical studies of the herbal combination showed decreases in triglycerides by 46.44%; LDL 36.89%; and cholesterol 35.19% in rats [7] and [8]. The results of the acute toxicity assay showed that the combination of *C. xanthorrhiza* extract and *G. procumbens* extract (1:4) did not have any toxic effect up to a dose of 2000 mg/kg. The histopathology results on the animal test did not show cellular changes or changes in the behavior of animals test [9]. Clinical trials of herbal products combined with *G.*

procumbens and *C. xanthorrhiza* have not been reported. Therefore this study is the first research on this herbal extract concerning its effect on hyperlipidemia in clinical setting.

The objective of this study is to determine the safety and efficacy of herbal product products compared to simvastatin with controlled clinical trials. The safety parameters of simvastatin and the herbal product were based on the results of hematological assessments, blood chemistry, and physical examinations before and after treatment. The efficacy parameters of simvastatin and the herbal product were based on the decrease in total cholesterol, LDL, and triglycerides, and increase in HDL.

2. Materials and Methods

Herbal product contains the main ingredients of *G. procumbens* leaves extract and *C. xanthorrhiza* rhizome extract combination (4:1). Herbal product was produced by PT Phapros Tbk. Simvastatin 10 mg was purchased from Kimia Farma. The research used a experimental design with a pre and post-control group, in a randomized controlled trial with open label. Prior ethical clearance was obtained from the Medical and Health Research Ethics Committee of the Faculty of Medicine Universitas Gadjah Mada with approval number: KE/FK/1044/EC/2016.

2.1 Inclusion and Exclusion Criteria

The inclusion criteria were adult dyslipidemia patients with a wash out period of 1 week for any anti-dislipidemia drugs prior the study, ages 20-60 years, male or female, patients with cholesterol levels total was ≥ 200 mg/ dL, LDL level ≥ 130 mg/dL, HDL level ≤ 40 mg/dL, triglyceride level ≥ 150 mg /dL, and were willing to join the research by signing an informed consent form. The exclusion criteria were subjects who are pregnant or planning pregnancy, breastfeeding, patients suffering from severe chronic diseases such as uncontrolled asthma, heart, kidney, or hematological disorders, metabolic or gastrointestinal problems, smoking, consuming alcoholic beverages and/or using other drugs in the past 1 week before and during clinical trials. The withdrawal criteria were those who resigned from clinical trials at their own request, did not comply with the rules agreed in clinical trials, used research products less than 80%, experienced side effects that did not allow patients to continue clinical trials, and disappeared or were difficult to contact.

2.2 Research procedures

The randomized controlled trial with open label started by dividing 50 subjects into 2 groups: Group I received simvastatin with dose of 10 mg/day and Group II received herbal product with dose of 60 mL (3x2 sachets @10 mL)/day for 30 days. The safety of the treatments was evaluated with physical and laboratory examinations, and the assessments of vital signs were performed before and after treatment. The patients underwent the physical and laboratory examinations at the Nayra Medika clinic in Pati, Central Java, Indonesia to establish a diagnosis of dyslipidemia and health condition. Patients also performed hematology tests (Mindray blood hematology analyzer BC-2600, England) and blood chemistry to measure liver and kidney function, triglyceride levels, total cholesterol, HDL, LDL, (Mindray chemical analysis BA-88A, China) and comorbidities. Patients who previously received anti-dyslipidemia drugs were provided a wash out period for one week before treatment. After treatment was given, monitoring of possible side effects was performed done routinely. The test subjects completed a form to record medication adherence, diet, exercise performed, and perceived effects other than usual while receiving the treatments for 30 days. On the 31st day physical and hematology examinations were conducted at the Nayra Medika clinic in Pati, Central Java, Indonesia related to the lipid profile and health condition of the patient. An interview was also conducted to obtain any additional data needed.

Subjects who met the inclusion criteria were given the treatment of simvastatin medication or herbal product extract according to the study design that had been determined. This research was conducted in Nayra Medika Clinic, Pati, Central Java, Indonesia. Subjects included in the herbal product group or positive control group were determined by random allocation. The steps before randomization were to make sequences (block variations) of the interventions to be given. The subject sampling sequence was obtained from random data generated by a computer program (Excel rand between, MicroSoft, Inc.) by providing a code number for the subject.

2.3 Statistical analysis

All data from examination results during clinical trials on subjects included the results of physical examination, side effects, and tabulated laboratory results. Data were analyzed using SPSS 22 (IBM Corp.,Chicago) statistical software. Characteristic data were analyzed using chi-square (if 2x2 tables) or Mann-Whitney (if 2xK tables) tests to determine the proportion between simvastatin and herbal product extract. Normality test was conducted using the Shapiro-Wilk test, with $p>0.05$ to show normally distributed data. Side effects (subjective symptoms) were recorded and analyzed descriptively (percentage of events). Data before and after treatment in each group were analyzed using paired_t-tests for normally distributed data and Wilcoxon tests for data which were not normally distributed. Comparison of the two treatment groups was tested with independent t-tests for data that was normally distributed and Mann-Whitney tests for data that were not normally distributed with a 95% confidence interval ($p<0.05$).

Lifestyle is a part of the confounding variables, because it may affect the results of the study. The record results of the records of the foods consumed by the test subjects were calculated for content of calories and fat and then compared to the recommended caloric needs of the test subject. The calorie requirements were calculated using the Harris Benedict formula. Meanwhile, in determining the fat requirement, it used the guideline by the World Health

Organization (WHO) at 10% of the total energy requirement. Compliance with test subjects in taking the medicine was also one of the confounding variables. In this study to improve the compliance of test subjects in taking medication by recording the drug taking card, the test subjects were contacted by researchers with telecommunication equipment at the time of taking medication. Furthermore, the test subjects were sent a report when taking medication via message or telephone, and asked to bring the packaging and any remaining medication to monitoring interviews. Drug adherence was assessed using the Morisky Medication Adherence Scale (MMAS-8) questionnaire.

3. Result and Discussion

Initial peripheral blood tests were performed on 200 subjects in order to obtain 127 subjects with high cholesterol levels. The subjects were then screened to obtain 54 test subjects who met the inclusion criteria. Subjects who met the inclusion criteria as many as 54 people were divided into 2 groups: the group that received the simvastatin drug and the group that received herbal product. Finally, 50 test subjects were obtained for analysis.

3.1 Characteristics of Subjects

The characteristics of the subjects (data not displayed) show that there were no significant differences ($p>0.05$) between simvastatin and herbal product groups, including level of age, sex, body mass index (BMI), level of education, occupation, comorbidities, and duration of dyslipidemia. It indicate that there were similarities in the proportion of subject characteristics in both groups. Comorbid conditions of subjects were gout and hypertension. Characteristics of subjects did not influence the final results of the study. Recent research affirmed that comorbid factors can reduce the potential for survival compared to patients without comorbidities [10] and [11].

Most of the test subjects were obedient in consuming the test drug, and the percentage of adherence in the simvastatin group was 56% (high) and 32% (medium) while the herbal product group was 52% (high) and 32% (medium). High and medium categories were based on the assessment of the MMAS questionnaire, however the subjects consumed all the simvastatin drugs according to the recommendations (30 tablets for 30 days). Table 1 shows that compliance in the simvastatin and herbal product groups had $p>0.05$. It means that the proportion of lifestyle and adherence was not significantly different, meaning that lifestyle and compliance did not affect the final results of the study.

In a meta-analysis of randomized controlled trials by Kelley et al. in 700 men and 88 women showed that diet and combination of diet and aerobic exercise had a significant effect in reducing total cholesterol, LDL and triglyceride levels [12]. Meanwhile, aerobic exercise can only reduce triglyceride levels and had no significant effect on HDL levels. Table 2 shows no significant differences in hematology value, lipid profile, blood chemistry, and vital sign parameters before treatment between in simvastatin and herbal product groups ($p>0.05$), except mean corpuscular hemoglobin concentrate (MCHC) ($p<0.05$). Hence, treatment results can be compared between the two groups.

3.2 Efficacy

The results of the statistical analysis of before and after treatment from the simvastatin and herbal product groups can be seen in Table 3. The results of statistical analysis simvastatin groups with $p<0.05$ in parameters of total cholesterol and LDL showed decreases total cholesterol and LDL levels that were statistically significant between before and after treatment. Meanwhile, the parameters which resulted in $p>0.05$ were triglycerides and HDL cholesterol. Simvastatin clinically can decrease total cholesterol and LDL values. The results of statistical analysis in herbal product groups with $p<0.05$ were triglycerides, HDL, and LDL which showed a decrease in triglyceride levels and a statistically significant increase in HDL and LDL between before and after treatment. The parameters which resulted in $p>0.05$ were total cholesterol, which showed an increase in cholesterol levels that were not statistically significant between before and after treatment. These results clinically indicate that the herbal product has an effect in reducing triglyceride levels and increasing HDL levels. However, the LDL value that was expected to drop instead showed an increase.

The results of statistical analysis between simvastatin and herbal product can be seen in Table 4. The result of statistical analysis with $p>0.05$ was HDL cholesterol which indicated that there was no significant difference between simvastatin and herbal product groups. Based on these results, the simvastatin and herbal product extract groups have the same efficacy increasing HDL cholesterol, but have different efficacy in reducing total cholesterol, LDL, and triglycerides.

The efficacy of the results of this study showed that simvastatin clinically and statistically significantly reduced cholesterol and LDL levels. The efficacy of herbal product indicated it was statistically and clinically effective in reducing triglyceride levels. Jones et al. reported that simvastatin dosages of 10-80 mg can reduce LDL cholesterol 12% to 18% in test subjects who were treated for 6 weeks [13]. Simvastatin dosage 20 mg can reduce LDL cholesterol 37%, total cholesterol 26, triglyceride 14%, and increase HDL cholesterol 4% in test subjects who were treated for 12 weeks with mild and moderate hypercholesterolemia [14] and [15]. This research obtained decrease in LDL 18.16%; total cholesterol 14.08%; triglyceride 11.41%; and HDL 1.3% in the simvastatin group. The herbal product groups obtained decrease in triglyceride 22.4%; increases in total cholesterol 1.46%; HDL 7.79%; and LDL 5.59%. The result of the study for the herbal product was no effect significant for total cholesterol and LDL. It can be caused by the antioxidant activity of *G. procumbens* and *C. xanthorrhiza* water extracts which have weak antioxidant activity, exceeding 200 µg/mL [16] and [17]. Free radicals can oxidize nucleic acids, proteins, lipids, and DNA causing

degenerative diseases, one of which is dyslipidemia [18]. Moreover, lipid profiles were still above normal value due to lack of sufficient dose and duration of treatment with the herbal product.

One of the ingredients of *C. xanthorrhiza* rhizoma is curcumin. In a study conducted by Soni and Kutan, it found that curcumin could reduce serum cholesterol and lipid peroxide levels in 10 human subjects given a dose of 500 mg/day for 7 days [19]. Results of the research showed decrease in serum levels of lipid peroxide (33%), an increase in HDL cholesterol levels (29%), and decrease in serum levels of total cholesterol (12%). Curcumin can increase HDL in hypercholesterolemia rats. Curcumin activates the rate-limiting step in cholesterol catabolism through cholesterol 7-α-hydroxylase stimulating the conversion of cholesterol to bile acid and degradation of cholesterol [20]. Curcumin also activates significant absorption of LDL and its action resembling a signal that opens the expression system of LDL receptors [21]. Production of 10 µM curcumin can inhibit LDL oxidation of 40-85%. Moreover, curcumin can reduce cholesterol and triglyceride levels in rabbits for 7 weeks at a dose of 3.2 mg. Curcumin also has the ability to inhibit the activity of acyl CoA in the liver [22].

Lokhande et al. showed that *G. procumbens* life-saving can suppress harmful microflora, reduce cholesterol levels of birds given egg yolk diet, and increase flight strength [23]. One of the ingredients of *G. procumbens* leaves is quercetin. Research by Sun et al. reported that quercetin can reduce cholesterol levels by inducing the expression of ABCA1 (ATP binding cassette transporter A1) on various THP-1 cells and increasing the flow of cholesterol from THP cells (cell proliferation). Moreover, quercetin can activate the PPARγ-LXRα (peroxisome proliferator activated receptor X-liver X receptor) pathway to rearrange ABCA1 expression, thereby increasing protein levels and transcription activity [24]. Ali et al. reported that *G. procumbens* can reduce glucose, cholesterol and triglyceride levels [25].

3.3 Adverse Events

Assessment of objective data with hematology, blood chemistry, and vital sign parameters. Blood chemistry includes lipids profile, liver function, and kidney function. Table 5 shows that simvastatin groups has $p<0.05$ in measurements of granulocytes mid, lymphocytes mid, platelet (PLT), and procalcitonin (PCT). It means that there were statistically significant differences before and after treatment. The administration of simvastatin before and after treatment provided a clinical impact on the subject. Although values of granulocytes mid, lymphocytes mid, PLT, and PCT were significantly different, their values were still in the range of normal values, so the treatment was considered safe for consumption. Table 5 shows that the herbal product groups have $p<0.05$ were granulocytes mid and lymphocytes mid. Although granulocyte mid and lymphocyte mid values were significantly different, their values were still in the normal range, so they were considered safe for consumption. The results delta mean of laboratory tests on blood chemistry, hematology, and vital sign shows $p>0.05$ (data not displayed), which indicates that there was no statistically significant difference between the simvastatin and herbal product groups. Simvastatin and herbal product before and after treatment did not have any clinical impact on the subjects.

The results of this study indicate that the simvastatin treatment has significant effect on hematological data, including PLT, PCT, granulocyte mid, and lymphocyte mid, but clinically it does not have an effect because it is still in the normal range. The herbal product group showed significant differences in hematological data, including granulocytes mid and lymphocytes mid but their values were still in the normal range. There are simvastatin (3 subjects) and herbal product (6 subjects) subjects taking drugs other than test drugs to overcome their complaints, i.e paracetamol dose 500 mg with duration of drinking between 2-3 days (1-3 tablets/day). One of the adverse events of simvastatin was cough and runny nose [26] and [27], so there were 3 subjects taking other drugs i.e paracetamol combination (Mixagrip®/Ultraflu®/Hufagrip forte®) to overcome these complaints. The drug was consumed for 2-4 days (1 tablet/day). Some of study showed that paracetamol can affect hematological data i.e MCH, MCHC, hemoglobin, leukocytes, and thrombocytopenia [28], [29], and [30]. This research shows that paracetamol adverse events on hematology can affect levels of granulocytes mid, lymphocytes mid, and PLT (platelets), so that a significant reduction in hematological data in the simvastatin or herbal groups can be caused by the use of paracetamol.

Statin drugs are widely chosen for the treatment of dyslipidemia, but there are some side effects which are inflammation of the muscles (0.5%), myalgia (2-10%), rhabdomyolysis with acute renal failure (0.1%), and liver function disorders (1-3%). Simvastatin group showed that significant differences in PCT which can be caused one of the side effects that is simvastatin symptoms of the subject comorbidities, i.e gout [15],[31], and [32] . The vital signs and physical examination of the simvastatin and herbal product group showed no statistically or clinically significant differences.

The administration of curcumin at a dose of 80 mg in 12 healthy subjects showed no side effects [33]. Research on 8 healthy subjects with a dose of 2 grams of curcumin orally did not show adverse effects. Phase 1 of clinical trials in 25 subjects who received curcumin 8 g/day for 3 months with a high risk of cancer showed no toxic reaction [34]. In another clinical trial study, 2 of 19 patients treated with curcumin 2500 mg/day complained of gastrointestinal irritation [35] and [36]. The toxicity test of *C. xanthorrhiza* water extract at a dose of 2 gr/kg BW did not show signs of toxicity in mice or rats. Median LD50 (lethal dose) of curcumin was more than 2 gr/kg BW given orally to mice [37]. Research on the acute toxicity of *G. procumbens* leaves in mice for 14 days did not show mortality or signs of toxicity up to a dose of 5 g/kg [38]. Research on the acute and subchronic toxicity of extracts and fractions of *G. procumbens* leaves showed that up to a dose of

2000 mg/kg, extracts and fractions were safe and did not show toxic effects [39].

Data of subjective symptoms if sorted from the greatest percentage of adverse events of the two groups were dizziness in 52% in the simvastatin group and 28% in the herbal product group. Dizziness complaints towards subjects can be caused by symptoms of dyslipidemia, one of the adverse events of simvastatin, and symptoms of the accompanying disease, which is hypertension [15], [32], [40], [41], and [42].

The in vivo bioavailability of the complex, such as in foods, herbs, and fermented products has become a concern of many research [43]. Testing of herbal ingredients consists of many and multiple materials that need a high amount to test whether the herbal treatments possibly have an effect. Limitations of this research were the study's short duration (30 days) which could affect the efficacy and safety. Moreover, the majority of the test subjects worker as a farmer (44% simvastatin group and 40% herbal product group) so the results might be different was it applied to subjects in the city. Another limitation was the dyslipidemia experienced by subjects which was mild so results would be different if applied to subjects with moderate or severe dyslipidemia. Furthermore, the comorbid conditions experienced by test subjects can influence the occurrence of side effects and subsequent test drug complaints. Additionally, the number of samples used was small so that in the future it is recommended to conduct trials with a larger number of samples. The duration of therapy and test drug dosage were also lacking so that the results obtained clinically were still above normal. Finally, the lipid profile used in this research was only 4 categories, so it is recommended for follow-up research to add apolipoprotein a, apolipoprotein b, VLDL, CPK, and using a negative control group or placebo.

4. Conclusion

The efficacy of the clinical trial result in the simvastatin group was significant ($p<0.05$) in reducing total cholesterol and LDL levels, but the treatment had no effect on triglycerides and HDL cholesterol. In the herbal product group, the treatment results were significant in reducing triglycerides and increasing HDL which had the same efficacy ($p>0.05$) in increasing HDL cholesterol but different efficacy in reducing total cholesterol, LDL, and triglycerides. Both treatments were considered safe for consumption, although some hematological results had significantly different results but were still in normal range. The most common adverse event of both groups was dizziness. Simvatatin could reduce total cholesterol and LDL but clinically, the levels were still above normal range. The herbal product could reduce triglyceride levels but clinically, the levels were still above normal range. The follow-up research can use a larger sample size with additional time to the duration of therapy, and increased treatment dosage. Furthermore, the combination of herbal extract can be made into other forms such as capsules, tablets, and caplets.

5. Acknowledgement

The researchers would like to thank the Ministry of Research and Technology of Higher Education for funding this research through the doctoral dissertation Research Grant Program Number: 102/ H-6/LPPM/STIKES-M/I/2018 on behalf of Endang Setyowati, MSc.,Apt. We also thank the Pharmaceutical doctoral program, Faculty of Pharmacy Universitas Gadjah Mada for their assistance in conducting this research. We also thank to Prodia laboratory for validity test (data not displayed) and Nayra Medika for clinical trial.

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Table 1: Proportion analysis of lifestyle and compliance in simvastatin and herbal product group

Life Style/Compliance	*Simvastatin n = 25*	*herbal product n = 25*	*p*
Estimated caloric intake[a]			
a. Corresponding	22 (88%)	19 (76%)	0.46[a]
b. Not appropriate/excessive	3 (12%)	6 (24%)	
Estimated lipid intake[a]			
a. Corresponding	25 (100%)	25 (100%)	1.00[a]
b. Not appropriate/excessive	0 (0%)	0 (0%)	
Physical activities[b]			
a. Bad	10 (40%)	11 (44%)	0.59[b]
b. Less	11 (44%)	12 (48%)	
c. Enough	4 (16%)	2 (8%)	
d. Very good	0 (0%)	0 (0%)	
e. High	0 (0%)	0 (0%)	
Compliance taking test drug[b]			
a. Low	3 (12%)	4 (16 %)	0.72[b]
b. Medium	8 (32%)	8 (32%)	
c. High	14 (56%)	13 (52%)	

Note: [a]: Chi Square test; [b]: Mann-Whitney test

Table 2: Baseline characteristic of hematology, lipid profile, bloof chemistry, and vital sign parameters before treatment in simvastatin group and herbal product group

Parameters	*Simvastatin n = 25 Mean ± SD*	*herbal product n = 25 Mean ± SD*	*p*
Total Cholesterol (mg/dL)	233.24 ± 19.96	200.40 ± 35.34	0.28[b]
Triglycerid (mg/dL)	172.84 ± 39.39	153.12 ± 45.03	0.19[b]
HDL (mg/dL)	36.92 ± 2.37	37.40 ± 7.36	0.59[b]
LDL (mg/dL)	161.84 ± 19.42	132.44 ± 25.89	0.48[b]
SGOT (U/L)	19.60 ± 3.63	20.28 ± 4.99	0.67[a]
SGPT (U/L)	19.56 ± 2.89	20.80 ± 4.83	0.29[a]
Ureum (mg/dL)	24.04 ± 6.76	23,96 ± 6,19	0.91[a]
Creatinin (mg/dL)	1.04 ± 0.07	1.05 ± 0.11	1.00[a]
Hemoglobin (g/dL)	12.96 ± 0.96	13.62 ±1.48	0.07[a]
WBC ($x10^3/\mu L$)	7.62 ± 1.50	8.16 ± 1.57	0.14[a]
HCT (%)	41.98 ± 2.84	43.12 ± 4.12	0.27[a]
PLT ($x10^3/\mu L$)	244.96 ± 53.67	243.16 ± 44.27	0.90[a]
RBC ($x10^6/\mu L$)	4.70 ± 0.33	4.83 ± 0.49	0.29[a]
MCV (fL)	89.44 ± 4.55	88.75 ± 4.80	0.46[a]
MCH (pg)	27.92 ± 1.19	27.89 ± 1.69	0.75[a]
MCHC (g/dL)	30.90 ± 0.54	31.59 ± 1.01	0.01[a*]
Granulocyte ($x10^9/\mu L$)	4.56 ± 1.26	5.19 ± 1.99	0.52[a]

Granulocyte mid (%)	8.02± 2.45	7.12 ± 1.62	0.14[a]
Granulocyte (%)	59.97 ± 6.22	60.45 ± 7.03	0.40[a]
lymphocyte (x10^9/L)	2.54 ± 0.82	2.53 ± 0.75	0.97[a]
lymphocyte mid (%)	0.64± 0.32	0.62± 0.22	0.59[b]
lymphocyte (%)	32.59 ± 6.01	31.66± 6.71	0.78[a]
RDW-CV (%)	13.69 ± 0.92	13.73 ± 0.75	0.89[a]
RDW-SD (fL)	46.82 ± 3.17	45.96 ± 3.75	0.39[a]
MPV (fL)	9.42± 0.55	9.28± 0.57	0.39[a]
PDW (%)	14.69± 0.30	14.59 ± 0.22	0.22[a]
PCT (%)	0.23 ± 0.05	0.23 ± 0.04	0.74[a]
Weight (kg)	59.8 ±10.12	58.88 ± 9.69	0.75[a]
Systolic blood pressure (mm Hg)	131.60 ±25.40	124.00 ± 17.44	0.23[a]
Dyastolic blood pressure (mm Hg)	82.40±11.06	80.40±11.83	0.55[a]
Pulse (x/minutes)	79.16 ± 2.46	79.92 ± 0.79	0.72[b]
Respiratory rate (x/minutes)	22.00 ±1.44	21.64 ± 1.16[b]	0.42[b]
Temperature(°C)	36.19±0,27[b]	36.16 ± 0.26[b]	0.53[b]

Note: a :Independent t-test; b: Mann-whitney test; *= significant (p<0,05)

Table 3 : Efficacy of research on lipid profile in simvastatin and herbal product groups

Parameter	*Simvastatin*			*herbal product*		
	Before treatment n = 25 Mean ± SD	*After tretment n = 25 Mean ± SD*	*p*	*Before treatment n = 25 Mean ± SD*	*After tretment n = 25 Mean ± SD*	*p*
Total cholesterol (mg/dL)	233.24 ± 19.96	200.40 ± 35.34	0.00[a*]	229.76 ± 16.92	233.12 ±25.36	0.49[a]
Triglycerid (mg/dL)	172.84 ± 39.39	153.12 ± 45.03	0.07[a]	189.64 ± 59.77	147.16 ± 35.73	0.00[b*]
HDL (mg/dL)	36.92 ± 2.37	37.40 ± 7.36	0.75[a]	36.44 ± 2.73	39.28 ± 8.49	0.05[a]
LDL (mg/dL)	161.84 ± 19.42	132.44 ± 25.89	0.00[a*]	155.72 ± 10.98	164.44 ± 28.75	0.04[b*]

Note : [a] paired t-test; [b] Wilcoxon test; *= significant (P<0,05)

Table 4: Mean difference in lipid profile between simvastatin and herbal product groups

Parameter	*Simvastatin n=25 Mean±SD*	*herbal product n=25 Mean ±SD*	*p*
Total cholesterol	32.84 ± 37.68[b*]	-3.36± 23.29[b*]	0.00[b*]
Triglycerides	19.72 ± 51.17[b*]	42.48± 59.08[b*]	0.04[b]
HDL	0.48 ± 7.22[a]	2.84± 6.69[a]	0.25[a]
LDL	29.40 ± 28.02[a*]	-8.72± 25.65[a*]	0.00[a*]

Note: [a] Uji independent t-test; [b] Mann-whitney test; *=significant (P<0,05)

Table 5 : Adverse events of hematology, blood chemistry, and vital sign in simvastatin and herbal product groups

Parameter	*Simvastatin*			*herbal product*		
	Before treatmentn = 25 Mean ± SD	*After treatment n = 25 Mean ± SD*	*p*	*Before treatmentn = 25 Mean ± SD*	*After treatment n = 25 Mean ± SD*	*p*
SGOT (U/L)	19.60 ± 3.63	19.92 ± 3.54	0.55[a]	20.28 ± 4.99	20.72 ± 3.67	0.41[a]
SGPT (U/L)	19.56 ± 2.89	19.20 ± 3.02	0.44[a]	20.80 ± 4.83	20.28 ± 4.79	0.33[b]
Ureum (mg/dL)	24.04 ± 6.76	23.24 ± 1.52	0.08[b]	23.96 ± 6.19	24.14 ± 5.56	0.61[b]
Creatinin (mg/dL)	1.04 ± 0.07	1.02 ± 0.07	0.22[b]	1.05 ± 0.11	1.04 ± 0.08	0.59[b]
Hemoglobin (g/dL)	12.96 ± 0.96	12.66 ± 1.15	0.16[a]	13.62 ±1.48	13.38 ± 1.53	0.38[a]
WBC (x10^3/µL)	7.62 ± 1.50	8.00 ± 2.23	0.32[a]	8.16 ± 1.57	8.14 ± 1.49	0.95[a]
HCT (%)	41.98 ± 2.84	41.43 ± 3.61	0.50[a]	43.12 ± 4.12	43.06 ± 4.64	0.94[a]
PLT (x10^3/µL)	244.96 ± 53.67	225.36 ± 41.83	0.02[a*]	243.16 ± 44.27	219.32 ± 54.07	0.08[a]
RBC (x10^6/µL)	4.70 ± 0.33	4.69 ± 0.53	0.94[a]	4.83 ± 0.49	4.85 ± 0.59	0.88[a]
MCV (fL)	89.44 ± 4.55	88.94 ± 4.75	0.41[a]	88.75 ± 4.80	88.78 ± 4.66	0.95[a]
MCH (pg)	27.92 ± 1.19	27.72 ± 1.04	0.34[a]	27.89 ± 1.69	27.63 ±1.75	0.21[a]
MCHC (g/dL)	30.90 ± 0.54	30.89 ± 0.73	0.93[a]	31.59 ± 1.01	31.48 ± 1.66	0.18[a]
Granulocyte (x10^9/µL)	4.56 ± 1.26	4.61 ± 1.36	0.85[a]	5.19 ± 1.99	4.88 ± 1.16	0.74[a]
Granulocyte mid (%)	8.02 ± 2.45	6.23 ± 1.33	0.00[a*]	7.12± 1.62	6.55 ± 1.01	0.04[a*]
Granulocyte (%)	59.97 ± 6.22	60.74 ± 6.44	0.56[a]	60.45 ± 7.03	59.92 ± 7.46	0.66[a]
lymphocyte (x10^9/L)	2.54 ± 0.82	2.53 ± 0.62	0.97[a]	2.53 ± 0.75	2.67 ± 0.75	0.47[a]
lymphocyte mid (%)	0.64± 0.32	0.47± 1.31	0.01[b*]	0.62± 0.22	0.52± 0.12	0.04[b*]
lymphocyte (%)	32.59 ± 6.01	32.50 ± 5.77	0.95[a]	31.66± 6.71	33.31 ± 7.35	0.25[a]
RDW-CV (%)	13.69 ± 0.92	13.65 ± 0.89	0.72[a]	13.73 ± 0.75	13.53 ± 0.95	0.07[a]
RDW-SD (fL)	46.82 ± 3.17	46.20 ± 2.65	0.27[a]	45.96 ± 3.75	45.83 ± 3.59	0.84[a]
MPV (fL)	9.42 ± 0.55	9.54 ± 0.61	0.31[a]	9.28± 0.57	9.35 ± 0.61	0.60[a]
PDW (%)	14.69± 0.30	14.80 ± 0.29	0.054[b]	14.59 ± 0.22	14.72 ± 0.33	0.14[a]
PCT (%)	0.23 ± 0.05	0.20 ± 0,04	0.01[a*]	0.23 ± 0.04	0.20± 0.05	0.06[a]
Weight (kg)	59.80± 10.12	59.48±10,02	0.19[a]	58.88 ± 9.69	58.60 ± 9.51	0.18[a]
Systolic blood pressure (mm Hg)	131.60 ±25.40	124.40 ± 20,80	0.12[a]	124.00 ± 17.44	120.00 ± 22.00	0.36[a]
Dyastolic blood pressure (mm Hg)	82.40 ±11.06	78.80 ± 11.07	0.13[b]	80.40 ± 11.83	77.20 ± 10.40	0.18[a]

Pulse (x/minutes)	79.16 ± 2.46	79.68 ± 3.82	0.64[b]	79.92 ± 0.79	79.16 ± 2.87	0.29[b]
Respiratory rate (x/minutes)	22.00 ±1.44	21.68 ±1.24	0.09[b]	21.64 ± 1.16	22.48 ± 0.92	0.06[b]
Temperature(°C)	36.19 ±0.27	36.11 ± 0.27	0.18[b]	36.16 ± 0.26	36.07± 0.39	0.53[b]

Note: [a] paired t-test; [b] Wilcoxon test; *= significant (P<0,05)