• pISSN: 2085-1545
• eISSN: 2339-093X

Sains Medika Journal of Medicine and Health

http://jurnal.unissula.ac.id/index.php/sainsmedika

RESEARCH ARTICLE

Allium sativum, Hylocereus polyrhizus and its Combination Effectiveness on Lipid Profiles and Number of Foam Cells in Rats with Dyslipidemia

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ABSTRACT

Introduction: *garlic extract (Allium sativum) and red dragon fruit extract (Hylocereus polyrhizus) have been used to improve lipid profile.* **Objective:** *to determine the effectiveness between garlic, red dragon extracts, and its combination on lipid profile and number of foam cells.*

Methods: *experimental study with a pre-test post-test control group design. Twenty five Wistar rats were divided into 5 groups: Group (Sim-G); Group II (BP-84), Group III (BN-84), Group IV (B P-BN), Group V (negative Control /Neg-G). All rats were fed a high cholesterol diet to induce dyslipidemia. On day 28, blood samples were taken for lipid profile evaluation. After termination, aortic blood vessels were subjected to foam cell evaluation.*

Results: *Post hoc test showed a significant decrease in total cholesterol, LDLc, Triglyceride and increase in HDLc in the treated groups compared to the negative control group ($p<0.05$. Mann Whitney test showed a significant differences in the number of foam cell in Sim-G, Gar-84, RD-84, dan Gar-RD compared to the Neg-G. There was a significant reduction in TC, LDLc, TG, and increase in HDLc in RD-84 compared to Gar-84 and Gar-RD. Foam cells number in Gar-RD insignificantly differ from Sim-G, $p>0.05$.*

Conclusion: *Red dragon fruit extract was more effective to lower lipid profiles compared to garlic extract. The combination of red dragon and garlic extract was more effective to reduce the number of foam cells compared to the extract of red dragon fruit and garlic extract alone.*

Keywords: *garlic extract, red dragon fruit extract, lipid profile, foam cell.*

ABSTRAK

Pendahuluan: Untuk memperbaiki profil lipid, masyarakat sering menggunakan ekstrak bawang putih atau ekstrak buah naga merah.
Tujuan: untuk mengetahui perbedaan efektifitas penggunaan ekstrak bawang putih, ekstrak buah naga merah, dan kombinasi keduanya terhadap perbaikan profil lipid dan jumlah sel busa.
Metode: penelitian eksperimental dengan PreTest PosTest Control Group Design, sebanyak 25 ekor tikus galur wistar dengan dislipidemia dibagi menjadi 5 kelompok. Kelompok kontrol negatif (Neg-G), Kelompok Simvastatin (Sim-G), kelompok ekstrak bawang putih 84 mg/BB (Gar-84), Kelompopk ekstrak buah naga merah 84 mg/BB (RD-84), Kelompok Kombinasi (Gar-RD). Hari ke 31 dilakukan pemeriksaan profil lipid, dengan spektrofotometer, kemudian tikus dimatikan diambil pembuluh darah aorta untuk pemeriksaan sel busa dengan pengecatan HE
Hasil: analisis Post Hoc menunjukkan bahwa terjadi penurunan signifikan kadar total cholesterol (TC), LDL kholesterol (LDLc), trigliserid (TG), dan peningkatan kadar HDL kholesterol (HDLc) pada Sim-G, Gar-84, RD-84, dan Gar-RD dibanding Neg-G, $p<0.05$. Analisis Mann Withney menunjukkan bahwa jumlah foam cell pada Sim-G, Gar-84, RD-84, dan Gar-RD dibanding Neg-G, $p<0.05$. Penurunan signifikan kadar TC, LDLc, TG, dan peningkatan kadar HDLc terjadi pada RD-84 dibanding Gar-84 dan Gar-RD. Namun Jumlah foam cell pada Gar-RD tidak berbeda bermakna dibanding Sim-G, $p>0.05$.
Kesimpulan: Pemberian ekstrak buah naga merah lebih efektif menurunkan profil lipid dibandingkan dengan ekstrak bawang putih dan kombinasi. Namun dalam menurunkan jumlah sel busa kombinasi bawang putih dan buah naga lebih effektif dibandingkan bawang putih dan buah naga secara tunggal. dengan ekstrak buah naga merah dan ekstrak bawang putih secara tunggal.

Kata kunci: ekstrak bawang putih, ekstrak buah naga merah, profil lipid,sel busa.

INTRODUCTION

High calorie intake can increase adipose tissue (overweight), changes in lipid profile and dyslipidemia (Dewi, 2016). Changes in lipid profile and serum lipoprotein can cause chronic diseases such as cardiovascular diseases and atherosclerosis, the leading cause of death worldwide (Salehi et al., 2015). In addition, the accumulated adipose tissue, especially visceral adipose tissue not only serves as source of energy but also produce proinflammatory cytokines such as IL-1, IL-6, and TNF α, triggering the liver to produce C reactive protein (CRP) (Gerner et al., 2013). High CRP levels can cause endothelial vascular damage leading to atherosclerosis (Dewi,

2016). The formation of foam cells indicate an early sign of atherosclerosis, formed when endothelial cells are activated by oxidized LDL. Circulating monocyte attached to activated endothelial, differentiate into macrophages before attaching to the endothelium and migrate to the tunica in become lipid-laden macrophage (Moore et al., 2013; Tabas and Bornfeldt, 2016; Yu et al., 2013). Therefore, the effectiveness of prevention and treatment of dyslipidemia is important because decrease in LDL levels by 1 mg/dL reduces the risk of cardiovascular disease by 1% (Adam, 2016).

Garlic (Allium sativum) extract has been shown to inhibit absorption of cholesterol by the intestine (Carotenuto et al., 1999) This effect has been associated with its contents sulfoxides such as (+)- S -(1-propenyl)-L-cysteinesulfoxide (PRENCSO), (+)-S -methyl-L-cysteinesulfoxide (MCSO), S -propropLcysteinesulfoxide, S -methyl-L-cysteine sulfoxide, and S -propropyl-L cysteinesulfoxide (Pareek et al., 2018). Other chemical compounds found in the extract of garlic include allicin (S -oxydiallyl disulfide), alliin (S -allyl-L-cysteine S -oxide), diallyldisulfide (allyldisulfide), S -methyl-L-cysteine S-dioxide (3-methylsulfinylalanine), propanethial S- dioxide (thiopropanal S- dioxide), and 3-mercapto-2-methypentan-1-ol (Rose et al., 2005). These compounds can inhibit the rate of cholesterol synthesis, through inhibition of reactions catalyzed by the enzyme hydroxymethylglutaryl-CoA (HMG-CoA) reductase (Gupta and Porter, 2001). Other evidence also shows that 1g/L garlic extracts can produce 50% inhibitory concentration (IC50) in the activity of the enzyme squalene mono-oxygenase, which plays a role in cholesterol biosynthesis. The working inhibitory reaction of the enzyme is irreversible (Gupta and Porter, 2001) so that the reduction in cholesterol levels is more stable.

Red dragon (Hylocereus p olyrhizus) fruit, contains antioxidant flavonoids anthocyanin (Bakar et al., 2011), have been shown to have an ability to inhibit cholesteryl esther protein transfer (CETP). CETP activity suppression, causing increased HDL cholesterol and decreased LDL cholesterol levels (Qin et al., 2009). Red dragon fruit also contains other antioxidants such as olcopersol, niacin, vitamin C, and even fiber which can reduce cholesterol levels in the blood. Efforts to reduce cholesterol are carried out by reducing the absorption and synthesis of cholesterol by inhibiting the activity of the HMG-CoA reductase enzyme in the liver. Tocopherol in dragon fruit extract has been shown to inhibit HMG-CoA reductase leading to reduced synthesis of endogenous cholesterol. In addition, anthocyanin have anti-inflammatory effect of inhibiting cytokines such as TNF-α. Decreased TNF-α leading to increase insulin sensitivity, increase fatty acid oxidation in the liver, inhibit cholesterol synthesis by liver cells, and reduce CRP production (Karlsen et al., 2007). The comparative effect between the administration of garlic and dragon fruit has not been established. The purpose of this study was to compare the effectiveness of the administration of garlic and dragon fruit extracts on lipid profile and the number of foam cells.

METHODS

This research was experimental study with the pre- post design control group design. Twenty five wistar rats aged 12-16 weeks with dyslipidemia were divided into 5 groups. Negative control group (Neg-C) was given distilled water. Simvastatin (Sim-G) was given simvastatin at a dose of 0.96 mg/ day. Group B (Gar - 84) was treated with garlic extract at the dose of 84 mg/ day. Red dragon fruit group (RD- 84) was treated with dragon fruit extract 84mg/day. Group combination of garlic and red dragon (Gar-RD) was treated with garlic and dragon fruit each at the dose of 42 mg/hour. All treatments were given once daily for 30 days. In the end of the study, blood and aortic blood vessels were taken for examination of lipid profile and number of foam cells. Lipid profiles and foam cells were evaluated using a spectrophotometer hematoxylin eosin (HE) staining respectively. This research was conducted after obtaining approval from the ethics commission of FK Unissula, Semarang.

Induction of Dyslipidemia in Rats

The rats were given a diet high in fat and high in cholesterol daily for 28 days. The diet consisted of 1% cholesterol, 5% egg yolk, 10% animal fat, 1% cooking oil, and standard diet to 100%. Before treatment, cholesterol, triglyceride, LDL, and HDL levels were evaluated in all rats. And also after the administration of high-fat and high-cholesterol diet for 28 days to ensure the success of dyslipidemia induction.

Preparation of Garlic and Dragon Fruit Extract

The garlic and red dragon fruit were sliced before dried in the oven at a maximum temperature of ±40°C. Dried materials were extracted using maceration with ethanol solvent with a ratio of 1:10 (weight/volume) for 48 hours. The material was filtrated and evaporated with rotary evaporator at ±40°C to obtain a thick extract. The thick extract is then weighed, recorded its weight and calibrated with the weight of the solvent in the same volume as the crude extract of the plant.

Dosage of Garlic Extract and Dragon Fruit

The dose of garlic extract based on the conversion of human doses (70 kg) to mice (200 g) was 0.018. The average human dosage is 300-1000 mg per day, which is generally used as a dose of 900 mg per day in the form of dry powder, whereas in studies using aged garlic extract (AGE) the dose used is even higher reaching 1-7.2 grams per day. In this study the dose was converted from a human dose of 1-7.2 grams so that the rat dose was obtained from 18-129.6 mg per day. Since the wide dose range, this study used median range doses of garlic extract and dragon fruit by 84 mg/200 gr BW.

Foam Cell Preparations

The paraffin block, which has been prepared, was fitted with a blade and set the tilt and the thickness of the tissue slice with the thickness of the incision. Then, the distance was adjusted of the end of the block with the blade; the safety under the pedal was opened. After that, the pedals backward to start cutting. Blok preparations are cut regularly and rhythmically, the band until discarded xylol 3, for 3 minutes. The preparation is dried, and then put into paraffin containing pieces of tissue was obtained. Pita transferred into a water bath tissue using a spatula. After expanded, the tissue band was attached to object glass coated with albumin to prevent the band from folding. Then the preparation was dried in the oven at 60 °C for 15 minutes before hematoxylin eosin (HE) staining. The preparation was added to xylol 1, xylol 2, and absolute alcohol, 80% alcohol, and 70% alcohol for 3 minutes. The preparations were then washed under running water for 5 minutes. After that, it was soaked in hematoxylin for 2-3 minutes, then wash with running water for 30 seconds, and define input into the concentrate for 30 seconds. After that define the rest of concentrate cleaned with running water for 30 seconds, and then added to the buffer concentrate blue for 30 seconds, then immediately cleaned with running water for 30 seconds. The preparation was then put into eosin for 1 minute, then into alcohol 70%, 80%, and absolute alcohol each for 2 minutes. Stains attached to the preparation are cleaned with tisue later dried. After dried, the preparation was added into xylol 1, xylolo 2, and xylol 3 for 2 minutes. The preparation is then dried and dripped with mounting media 1 drop, covered with dec glass, then observed under a microscope at 400 times magnification.

Statistical Analysis

To ensure that the administration of high-fat and high-cholesterol diet for 28 days before administration resulted in dyslipidemia, a statistical pair t-test was performed followed by ANOVA test to ensure that dyslipidemia among groups after given a high fat diet was not significantly different. After the treatment, the data on lipid profile was evaluated using the ANOVA test followed by Post Hoc test, considering the distribution of normal and homogeneous data. Kruskal-Wallis test was performed for foam cell variable, followed by Mann Whitney test considering that the data were not normal and homogeneous. The statistical significance was set at $p < 0.005$.

RESULTS

After the administration of a high fat and

Table 1. Lipid Profile & Foam Cells Following the administration of a High Cholesterol Diet and Treatment of Onion and Red Dragon Fruits Extract in Rats

Lipid Profile	Groups									
	Neg-G N= 6 χ (± SD)		Sim-G N= 6 χ (± SD)		Gar-84 N= 6 χ (± SD)		RD-84 N= 6 χ (± SD)		Gar-RD N= 6 χ (± SD)	
	Pre-treat	Post-treat	Pre-treat	Post-treat	Pre-treat	Post-treat	Pre-treat	Post-treat	Pre-treat	Post-treat
Cholesterol Total (mg/dl)	225.99 ± 4.72	228.39 ± 5.41	223.94 ± 3.77	104.94 ± 4.85	224.38 ± 3.81	133.80 ± 3.70	220.73 ± 3.52	113,88 ± 3.73	222.05 ± 5.17	150.43 ± 3.78
HDL Level (mg/dl)	25,57 ± 1.80	22.78 ± 1.13	25.88 ± 1.24	72.45 ± 2.99	24,16 ± 1.51	48.68 ± 2.96	24.78 ± 1.63	63.35 ± 3.45	24.79 ± 1.62	39.15 ± 2.07
LDL Level (mg/dl)	75.28 ± 3.04	78.05 ± 1.56	78,33 ± 1.42	27,59 ± 1.45	76.81 ± 1.94	48.36 ± 2.68	76.96 ± 2.71	38,47 ± 3.32	75.13 ± 1.97	61.60 ± 1.88
TG Level (mg/dl)	150,32 ± 4.33	150,32 ± 4.33	149,19 ± 2.73	94.31 ± 3.81	150.97 ± 5.74	120.00 ± 2.95	146,77 ± 2.73	109,64 ± 1.89	147,74 ± 6.99	135,19 ± 3.55
Foam Cell (Σ)	-	13.10 ± 1.14	-	2.60 ± 0.55	-	6.40 ± 1.14	-	6.80 ± 0.84	-	3.40 ± 0.55

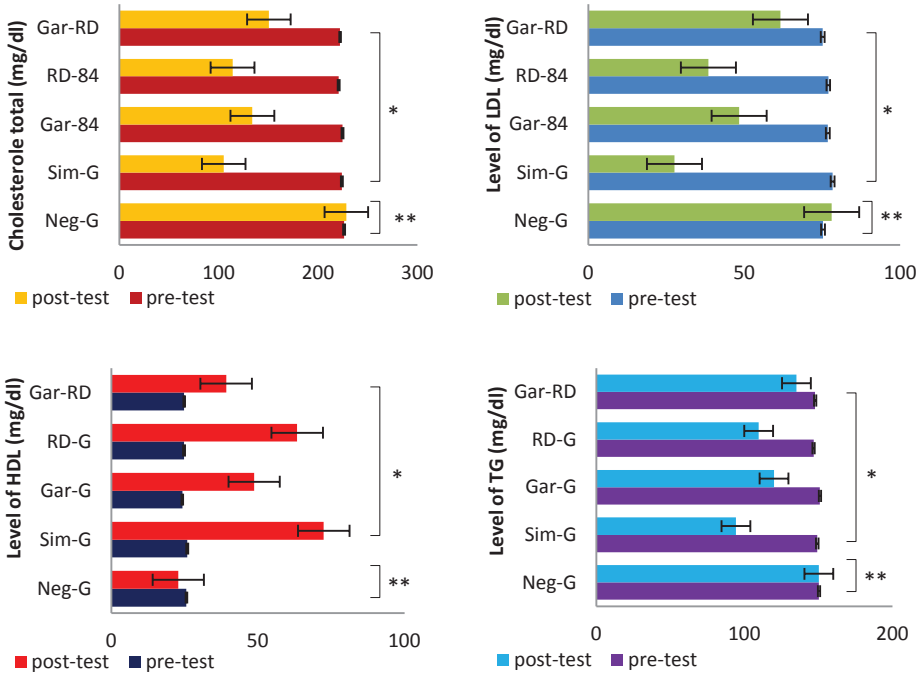

Figure 1. LDL levels and a significant decrease in post-test HDL levels, p <0.05 (figure 1).

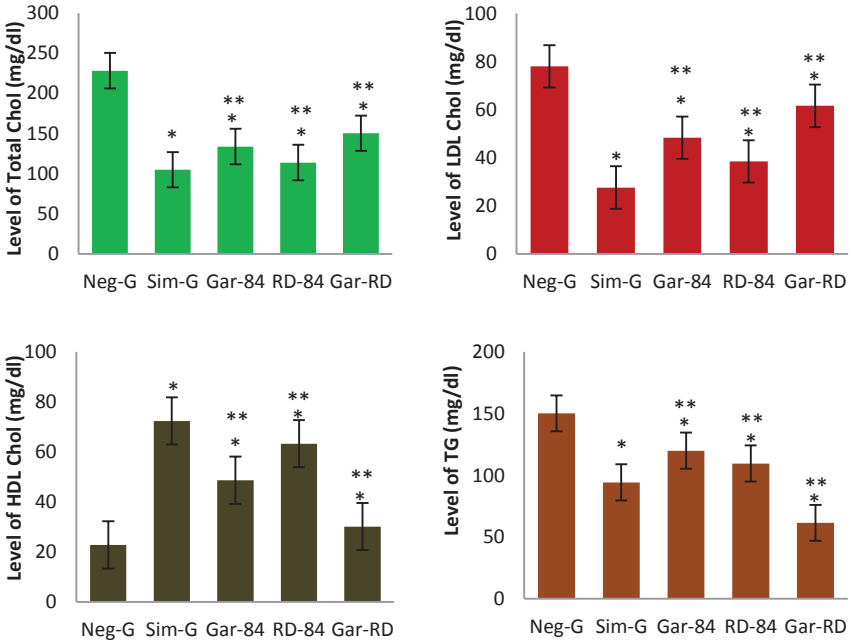

Figure 2. Level of Total Cholesterol, LDL Cholesterol, HDL Cholesterol, Triglyceride after the treatment in each Group. Post Hoc Analysis. * p<0.05 Neg-G as control ; ** p <0.05 Sim-G as control.

high cholesterol diet for 28 days (pre-test) and after administration of garlic extract, red dragon fruit alone and in combination for 30 days (post-test) obtained the mean of lipid profile is presented in the table 1.

To determine that total cholesterol, HDL, LDL, and triglyceride levels after the administration of a high cholesterol diet between groups were not significantly different, ANOVA statistical tests were applied. The ANOVA analysis results showed no significant differences between groups, p >0.05. This showed that lipid levels among groups were comparable. Thus, research proceeded with the administration of garlic extract, red dragon fruit alone and in combination extract to determine the most effective to improve lipid profiles.

After administration of garlic extract, red dragon fruit, and a combination of both for 30 days (post-test) the mean lipid profile was better than before treatment (table 1). To find out whether there is a significant improvement in lipid profile after administration of

garlic extract, red dragon fruit, and a combination of both of them compared to before, it is necessary to do a pair t-test.

Differences in Lipid Profiles before and after Treatment

The results of paired T test analysis showed that there was a decrease in total cholesterol , LDL, and triglyceride levels post - test in all four treatment groups (Sim-G, Gar-84, RD-84, and Gar-RD) compared to the pre -test, p <0.05. Conversely there was a significant increase in post-test HDL levels compared to the pre-test, p <0.05. Conversely in the Neg-G group there was a significant increase in total cholesterol and LDL levels and a significant decrease in post-test HDL levels, p <0.05 (figure 1).

This research illustrates that giving treatment with garlic extract, red dragon fruit, singly or in combination with a dose of 84 mg/day and administration of Simvastatin at a dose of 0.96 mg/day for 30 days can improve lipid profile.

Furthermore, the analysis using ANOVA test was applied to determine that there was a statistically significant difference in between groups after treatment. The results of ANAOVA test showed that there were significant differences in total cholesterol, LDL, HDL, and triglyceride levels between groups (p <0.05). To determine which groups with significant difference, LSD Post Hoc statistical tests were carried out.

Total Cholesterol Level

The results of the Post Hoc analysis showed that there was a significant decrease in total cholesterol levels in Sim-G, Gar-84, RD-84, and Gar-RD compared to Neg-G, p <0.05. Total cholesterol levels in Gar-84, RD-84, and Gar-RD increased significantly compared to Sim-G, p <0.05. Furthermore, total cholesterol levels in RD-84 decreased significantly compared to Gar-84 and Gar-RD (p <0.05) (figure 2).

LDL Cholesterol Level

The results of the Post Hoc analysis showed that there was a significant reduction in cholesterol LDL levels in Sim-G, Gar-84, RD-84, and Gar-RD compared to Neg-G, p <0.05. Levels of LDL cholesterol at Gar-84, RD-84 and RD-Gar increased significantly compared to Sim-G, P <0.05. Furthermore, LDL cholesterol levels in RD-84 decreased significantly compared to Gar-84 and Gar-RD (p <0.05) (figure 2).

HDL Cholesterol Level

The results of the Post Hoc analysis showed that there was a significant increase in cholesterol HDL levels in Sim-G, Gar-84, RD-84, and Gar-RD compared to Neg-G, p <0.05. HDL cholesterol levels in Gar-84, RD-84, and Gar-RD were significantly lower than Sim-G, p <0.05. Furthermore, HDL cholesterol levels in RD-84 increased significantly compared to Gar-84 and Gar-RD, p <0.05 (figure 2).

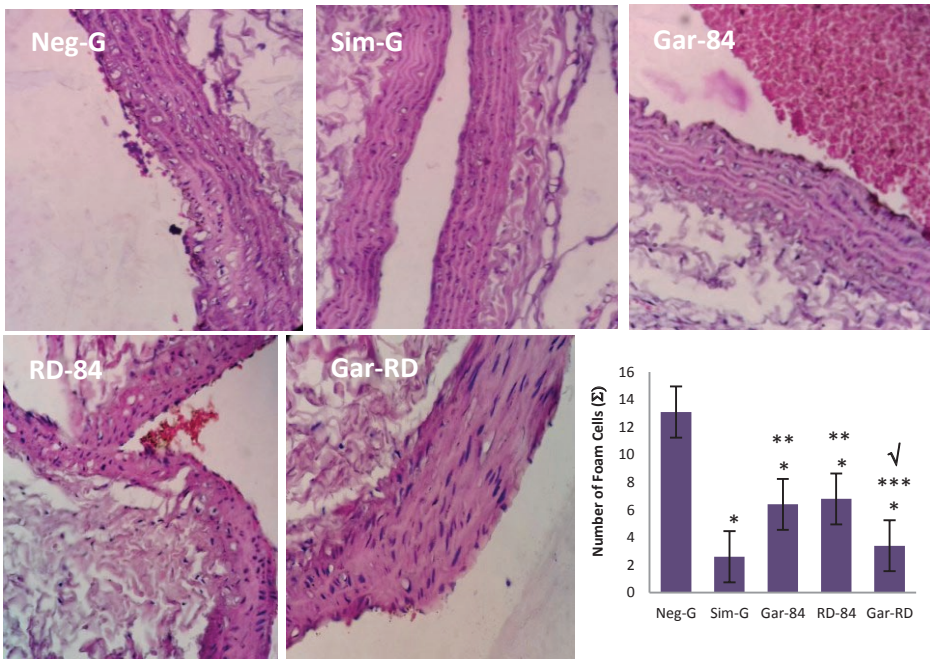

Figure 3. Number of Foam Cells after the Treatment in Each Group. Mann Withney Analysis: * p<0.05 Neg-G as control; ** p<0.05 Sim-G as Control; *** p<0.05 Gar-84 as Control; ✓ p > 0.05 Sim-G as Control

Triglyceride Level

The results of the Post Hoc analysis showed that there was a significant decrease in triglyceride levels in Sim-G, Gar-84, RD-84, and Gar-RD compared to Neg-G, $p < 0.05$. Triglyceride levels in Gar-84, RD-84, and Gar-RD increased significantly compared to Sim-G, $p < 0.05$. Furthermore, triglyceride levels in RD-84 decreased significantly compared to Gar-84 and Gar-RD, $p < 0.05$ (figure 2).

The Number of Foam Cells

The number of foam cells after the treatment with garlic extract, red dragon fruit alone and in combination for 30 days is presented in Table 1. The highest number of foam cells was found in Neg-G followed by RD-84, Gar-84, Gar-RD, Sim-G. The results of the Kruskal Wallis analysis showed that there were significant differences between groups ($p < 0.05$). To determine the groups with a significant difference, Mann Withney test was applied to the data analysis.

The results of the Mann Withney analysis showed that the number of foam cell in Sim-G, Gar-84, RD-84, and Gar-RD was significantly lower than that of Neg-G, $p < 0.05$. The number of foam cells in the Gar-84, and RD-84 was significantly higher than that of Sim-G ($p < 0.05$). The number of foam cells in Gar-RD was not significantly different compared to that of Sim-G, $p > 0.05$ (figure 3).

The results of this study showed that the administration of garlic extract, red dragon fruit alone and in a combination reduced the number of foam cells as effective as simvastatin.

DISCUSSION

The results of this study showed that the administration of garlic extract and red dragon fruit extract alone and in combination improved lipid profiles. Improvement of the lipid profile was defined as the decreased level of total cholesterol, LDL cholesterol, and triglyceride and increased levels of HDL cholesterol after the administration of a high-fat high cholesterol diet.

The administration of garlic extract at a dose of 84 mg/day was shown to reduce levels of total cholesterol, LDL cholesterol, and triglycerides and increase levels of HDL cholesterol. The result of this study supports that of systematic review and metaanalysis reported by Shabani E, et al. That garlic extract can reduce lipid profile, glucose, and treat patients with cardiovascular disease and diabetes (Shabani et al., 2019). In addition, the study conducted by Salehi I, et al. also showed that garlic extract effectively controls hyperlipidemia and has the potential to prevent atherosclerosis (Salehi et al., 2015). Likewise, the results of the meta-analysis conducted by Sun YE, et al. demonstrated that the administration of garlic extract reduces levels of TC and LDL, increase HDL levels and triglycerides (Sun et al., 2018).

The administration of red dragon fruit has been shown to reduce TC, LDL, and triglyceride levels, on the contrary increase HDL levels. The results of this study are in accordance with the study reported by Werdiningsih and Suhartati showing that the administration of red dragon fruit proved to be able to reduce TC, LDLc and triglyceride levels, on the contrary increasing HDLc levels (Werdiningsih and Suhartati, 2018). The study reported by Hadi NA, et al. also showed that administration of red dragon fruit extract at a dose of 600 g per day in patients with type 2 mellitus proven to reduce glucose levels, triglycerides, total cholesterol, and LDL, on the contrary increasing HDLc levels (Hadi et al., 2012).

Overall, the results of this study indicate that administration of red dragon fruit extract was more effective to improve lipid profile than garlic extract. Several other studies have even shown that red dragon fruit extract can reduce lipid profiles faster. Giving dragon fruit extract at a dose of 60 mg 1 time a day, has been shown to improve lipid profiles. The dose of 125 mg of garlic can reduce total cholesterol levels. However, the use of garlic with low doses (125 mg /kg BW), moderate dose (250 mg/kg BW), and high dose (500 mg/kg BW) can prevent hypercholesterolemia (Dewi, 2016).

Red dragon fruit was more effective that garlic because it contains anthocyanin. Anthocyanin is a type of flavonoids belonging to the family of polyphenols (Bakar et al., 2011). Anthocyanin has the ability to inhibit the activity of Cholesteryl ester transfer protein (CETP). As a result there was an increase in HDL levels and lower LDL levels (Qin et al., 2009). Red dragon fruit also contains antioxidants of tocopherol, fiber, niacin and vitamin C, besides being able to inhibit cholesterol absorption and reduce the synthesis of endogenous cholesterol catalyzed by HMG CoA reductase enzyme which is not activated by tocopherol. In addition, anthocyanin also have anti-inflammatory effects by inhibiting TNF-α, NF- κ B through the mitogen-activated protein kinase (MAPK). Thus, insulin sensitivity and fatty acid oxidation in the liver increases, inhibits cholesterol synthesis by liver cells, and reduces risk factors for cardiovascular disease (Karlsen et al., 2007; Lee et al., 2017).

Foam cells as precursors of atherosclerosis have

also been shown to decrease in number due to the administration of garlic and red dragon fruit extract. However, red dragon fruit extract is more effective in reducing the number of foam cells than garlic. This is because anthocyanin, but can increase the levels of HDLC and LDLC lowering, also shown to induce expenses (efflux) macrophage cholesterol mediated by activation of peroxisome proliferator activated receptor trajectory χ liver-X receptor α ATP-binding Cassette (ABCA-1) (Xia et al., 2005).

Overall the results of this study indicate that simvastatin is more effective to improve the lipid profile and the number of foam cells compared to extracts of garlic and red dragon fruit singly or in combination. However, the decrease in the number of foam cells in the administration of a combination of garlic extract and red dragon fruit is similar to simvastatin. This could be caused by a decrease in LDLc levels oxidized by antioxidants contained in garlic and dragon fruit (Lee et al., 2017).

CONCLUSION

The administration of garlic and red dragon fruit extract alone and in combination can improve lipid profile and number of foam cells. The administration of red dragon fruit extract was better in improving lipid profile than garlic extract and its combination red dragon fruit, but the combination of garlic extract and red dragon fruit extract was more effective in reducing the number of foam cells and as effective as simvastatin.

CONFLICT OF INTEREST

There is no conflict of interest

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