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THE EFFECTS OF SIMVASTATIN, ROSUVASTATIN, AND FENOFIBRATE ON THE BODY WEIGHT AND LIPID PROFILES OF FEMALE RATS TREATED WITH ORAL CONTRACEPTIVES AND A HIGH-FAT DIET

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ABSTRACT

This study aimed to compare the effects of simvastatin, rosuvastatin, and fenofibrate therapies on the body weight and lipid profiles of the female rats receiving a combination of oral contraceptives (COC) and a high-fat diet (HFD). Twenty female Wistar rats (130-200 g) were divided equally into four groups. The rats received a standard diet for seven days, and their baseline lipid profiles were analyzed. All rats also received COC containing 15.1 µg/kg levonorgestrel/3.1 µg/kg estradiol with HFD for 60 days. Starting on day 31, the rats were given the respected treatment. The control group received the vehicle, whereas the others were treated with either simvastatin (2.1 mg/kg), rosuvastatin (0.5 mg/kg), or fenofibrate (8.2 mg/kg). Blood samples were taken on days 30 and 60. The results showed that the administration of COC+HFD and vehicle for 30 days increased the rats' body weight and dyslipidemia, characterized by a significant decrease in Low-Density Lipoprotein (HDL) and an increase in total cholesterol (TC) and triglycerides (TG) levels ($P<0.05$). Among the treatments, only fenofibrate was found to be able to prevent a significant weight gain in rats. Both fenofibrate and rosuvastatin inhibited a significant rise in TG and TC levels. Meanwhile, the simvastatin administration failed to do the same. Although statistically insignificant, all treatments increased rats' HDL levels. Thus, it can be concluded fenofibrate was the most effective treatment among all in reducing weight gain and improving the lipid profile of dyslipidemic rats induced by oral contraceptives and a high-fat diet.

Key words: fibrate, high-fat diet, lipid profile, oral contraceptives, statin

ABSTRAK

Penelitian bertujuan membandingkan pengaruh terapi simvastatin, rosuvastatin, dan fenofibrat terhadap berat badan dan profil lipid tikus betina yang mendapat kontrasepsi oral kombinasi (COC) dan diet tinggi lemak (HFD). Tikus wistar betina (130-200 g) dibagi menjadi empat kelompok. Tikus menerima diet standar selama tujuh hari dan profil lipid awal dianalisis. Semua tikus menerima COC mengandung 15,1 g/kg levonegestrel/3,1 g/kg estradiol dengan HFD selama 60 hari. Hari ke-31, tikus diperlakukan sesuai dengan terapi yang diberikan. Kelompok kontrol menerima plasebo, sementara yang lain diobati simvastatin (2,1 mg/kg), rosuvastatin (0,5 mg/kg), dan fenofibrat (8,2 mg/kg). Pengambilan sampel darah dilakukan hari ke 30 dan 60. Hasil penelitian menunjukkan bahwa pemberian COC+HFD dan plasebo selama 30 hari menyebabkan peningkatan berat badan dan dislipidemia ditandai dengan penurunan Low-Density Lipoprotein (HDL) yang signifikan, peningkatan kolesterol total (TC) dan trigliserida (TG) tingkat ($P<0,05$). Diantara obat yang diberikan, fenofibrat ditemukan mencegah kenaikan berat badan yang signifikan. Baik fenofibrat dan rosuvastatin menghambat peningkatan kadar TG dan TC yang signifikan, sementara, simvastatin gagal melakukan hal yang sama. Meskipun secara statistik tidak signifikan, semua terapi meningkatkan kadar HDL tikus. Disimpulkan bahwa fenofibrat lebih efektif menurunkan berat badan dan memperbaiki profil lipid tikus dislipidemia yang diinduksi COC dan HFD.

Kata kunci: fibrat, diet tinggi lemak, profil lipid, kontrasepsi oral, statin

INTRODUCTION

Hormonal oral contraceptives are one of the methods used to prevent unwanted pregnancy by acting on the endocrine system. However, hormonal contraceptives have been reported to affect heart function, blood pressure (BP), fat, and carbohydrate metabolism (Sufa *et al*. 2019). Hormonal contraceptive pills generally consist of estrogen and progesterone (Al-Juhaishi *et al.* 2018). Estrogens are known to regulate many cellular functions and modulate cellular metabolic homeostasis. Estrogen acts on estrogen receptors and is known as an essential regulator of lipid metabolism. Estrogen regulates lipogenesis, lipolysis, and adipogenesis in adipose tissue (Kim and Park 2012).

Oral contraceptives alter lipid levels through a genomic pathway where estrogen influences the regulation or control of hepatic apolipoproteins (Aasare *et al*. 2014). Estrogen can increase triglyceride levels, increase high-density lipoprotein (HDL) and decrease low-density lipoprotein (LDL) levels (Dilshad *et al.* 2016). The use of hormonal contraceptives indirectly affects the mechanisms involved in weight gain and obesity (Kim and Park 2012).

Combined oral contraceptives containing synthetic progesterone and estrogen work by blocking the production of hormones produced by the ovaries. Although estrogen may protect against increased lipid metabolism, progesterone may dominantly elicit the adverse effects on lipid metabolism, including lowering HDL levels by increasing liver lipase activity. Androgenic progestogens may outweigh the beneficial effects of estrogen on lipid profiles; hence, the progesterone component in the contraceptive pill reduces the lipid-modulating effect of estrogen

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(Dilshad *et al.* 2016). Consequently, many women experience weight gain and lipid disorders due to combination of oral contraceptives (COC) administration.

Several therapies have been used to treat dyslipidemia, including those using statins and fibrates. These agents have different actions, and consequently, they may result in different outcomes on lipid profiles. It has been established that fibrates are more likely to reduce triglyceride and increase HDL levels in patients with diabetes or metabolic syndrome (Chen *et al.* 2013). Meanwhile, statins are more effective to reduce total cholesterol since it acts by inhibiting the enzyme 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA) reductase. Statins are also most likely to increase the number of LDL receptors on the liver cell membrane, which leads to reduced LDL levels (Stocco 2013). In the past few decades, it has been established that statins may create different effects based on their solubility. The lipophilic statins, such as simvastatin, diffuse passively into cells, while hydrophilic statins, such as rosuvastatin or pravastatin enter, elicit cellular effects via intracellular transport pumps (Chen *et al.* 2013).

Although simvastatin, rosuvastatin, and fenofibrate have been known as anti-dyslipidemic agents in general, their effects on COC-induced dyslipidemia have not been explored yet. COC-induced dyslipidemia has different pathomechanisms compared to dyslipidemia induced by increased consumption of fat or alcohol or diabetes mellitus. Therefore, it is interesting to explore the effect of simvastatin, rosuvastatin, and fenofibrate on weight gain and lipid profiles of rats induced by oral contraceptives and a high-fat diet. This study may find a clinical significance that benefits contraceptive users.

MATERIALS AND METHODS

Twenty female Wistar rats (*Rattus norvegicus*) weighing 130-200 g and aged 2-3 months old were used. The rats were obtained from a rat breeding facility in Maros Regency, South Sulawesi. They were adapted to the laboratory environment for seven days. During the adaptation process, the animals were given standard feed and tap water on a daily basis. Their general conditions were also closely observed. The environment in the cage was made as comfortable as possible by adjusting the temperature, humidity, and light intensity of the temperature required for the treatment of white rats (25-26° C), with an average humidity of 40-60%.

The rats' body weight was monitored daily before the treatments were administered. The animals were randomly grouped to ensure the variations in body weight did not exceed 20% of the average body weight. The high-fat feed was prepared from 100% duck egg yolk. The duck egg yolks were chosen because they have high cholesterol content (2,118 mg/100 g) which is much higher than that of chicken egg yolks (1,274-1,881 mg/100 g) (Chahyanto *et al.* 2016). The duck egg yolks were whisked and administered daily with a volume of 2 mL/200 g by using an oral canulae. After seven days of adaptation, all of the animals received COC containing 15.5 µg/kg levonorgestrel/3.1 µg/kg estradiol with a high-fat diet (HFD) for 60 days. The animals were then divided into four groups based on the therapies given following 30 days of COC and HFD administration. On day 31, the control group received vehicle (sodium carboxymethyl cellulose), whereas the others were treated with either simvastatin (2.1 mg/kg), rosuvastatin (0.5 mg/kg), or fenofibrate (8.2 mg/kg). Blood samples of the rats were taken before COC and HFD administration (day 0), after 30 days of COC and HFD administration (day 30), and after 30 days from treatment initiation (day 60). The blood samples were taken from the orbital vein and centrifuged for 20 minutes at 3000 rpm. The serum was collected, and lipid profiles, including HDL, triglyceride (TG), and total cholesterol (TC) levels, were analyzed using kit reagents with a photometric method (AutoAnalyzer Indiko, Thermo Scientific).

Data Analysis

The data were expressed as mean ± SD, and the data normality was analyzed using the Shapiro-Wilk test. Differences in HDL, TG, and TC levels before and after the administration of COC and HFD were analyzed using a paired t-test.

RESULTS AND DISCUSSION

Rats' Body Weight

One of the widely known side effects of hormonal contraceptives is weight gain. It is likely to occur because estrogen can cause water retention and edema. At the same time, progestagens facilitate the conversion of carbohydrates and sugars into fat and stimulate appetite and reduce physical activity (Hirscbberg 1998). Estrogen-induced weight gain is caused by increased subcutaneous fat (Mulazimah 2017). Changes in the body weight of rats can interfere with fat metabolisms, whereas excessive fat consumption exacerbates the lipid disorder. This process stimulates the mobilization of fatty acids to adipose tissue, which causes an imbalance in lipolysis and fat synthesis in the liver and body tissue (Yunita *et al*. 2020).

As seen in Table 1, there was an increase in the body weight of rats after the administration of contraceptive pills and a fat diet for 30 days, which occurred across the treatment groups. During 60 days of the experiment, rats gained weight and showed signs of obesity, The body weight and body length were used to determine the following anthropometrical parameters: Body mass index (BMI)= body weight (g)/length^2 (cm^2) and Specific rate of body mass gain (g/kg)= dM/M dt, where dM represents the gain of body weight during dt= t_2-t_1, and M is the rat body weight at t_1 (Novelli *et al.* 2007). Obesity occurs due to excess triglyceride stores in adipose tissues. The induction of a high-fat diet in rats increased body weight through modulation of the gut microbiota, resulting in increased intestinal permeability and absorption (Cani *et al.* 2008). The increase in free

fatty acids that accumulate in tissues will increase the accumulation of long-chain acyl-CoA and its metabolites, including diacylglycerol (DAG), triacylglycerol (TAG), and intracellular ceramides. The accumulation of ceramides triggers the dephosphorylation of protein kinase B/Akt. Dephosphorylation of PKB/Akt triggers glucose transport to tissues through increased glucose transporter-4 (GLUT-4), resulting in increased glycogenesis. PKB/Akt dephosphorylation also inhibits lipolysis and gluconeogenesis in tissues. Increased glucose uptake to tissues and glycogenesis and downregulation of lipolysis and gluconeogenesis leads to increased body mass (Lastra *et al.* 2014; Putri and Isti 2015).

In this study, the use of simvastatin, rosuvastatin, and fenofibrate for 30 days did not prevent weight gain in rats. However, only with fenofibrate administration, the body weight of rats was not increased significantly on day 60 compared to day 30. In contrast, rats receiving simvastatin or rosuvastatin continued to experience a significant weight gain after day 60 ($P<0.05$). This result may implicate that fenofibrate therapy was more suitable to prevent a significant weight gain for rats that were subjected to oral contraception.

HDL Levels of Rats

Estradiol reduces plasma cholesterol synthesis by inhibiting HMG CoA reductase, which is an enzyme that has an important role in cholesterol biosynthesis. The most common lipid changes seen in combined oral contraceptive users were an increase in LDL cholesterol (LDL-C) and a decrease in HDL levels.

Table 2 shows the HDL levels of treatment groups on days 0, 30, and 60 of the experiment. From days 0 to 30, the placebo group had decreased HDL cholesterol (HDL-C) levels ($P<0.05$). This shows that the administration of contraceptive pills and a high-fat diet for 30 days can reduce the serum HDL-C levels. Most groups also showed a reduction in HDL levels in the first 30 days of COC and HFD administration although these were not statistically significant ($P>0.05$). This may indicate that a longer induction time was necessary to obtain more significant results.

A previous study reported that adding 10% of fat to a standard pellet significantly reduced HDL levels of rats after introducing the high-fat diet for 30 days (Sitinjak, 2019). HDL-C is produced by the liver and intestines, serving as a transporter of cholesterol into the liver. Administering diets with high saturated fatty acids can suppress HDL synthesis by decreasing apolipoprotein A-1, a precursor for HDL formation. In addition, the decrease in HDL levels of rats observed in this study may also be triggered by progesterone present in COC, which stimulated hepatic lipase activity (Agung 2008). Several studies have found minimal reductions in HDL-C but no effect on other lipid metabolism parameters (Dixit and Jagan 2016).

Our data showed that after 30 days of treatment, the administration of simvastatin, rosuvastatin, and fenofibrate for 30 days caused slight increases in HDL levels of about 14%, 13%, and 18%, respectively. However, none of these was significant ($P>0.05$) compared to day 30 before the rats received the treatments. A longer duration or a greater dose of therapies might be necessary to obtain a significant increase in serum HDL-C levels in the rats.

A previous study revealed that combined oral contraceptive and a high-fat diet administration for

Table 1. The effects of statins or fibrate treatment on rats' body weight

Treatment	Body weight (g)			% Change±SD	P-Value (Paired t-test)	P-Value (one way ANOVA)
	Day 0	Day 30	Day 60			
COC+HFD+ Vehicle	151±10.8	178.2±9.9	185.6±9.4	18±8.9 (a) 4.1±1.3 b	0.008 (c) 0.001 (d)	
COC+HFD+ Simvastatin	152±10.1	174.2±13.1	179.4±11.8	14.6±5.8 (a) 2.9±2.6 (b)	0.004 (c) 0.049 (d)	0,110 (e)
COC+HFD+ Rosuvastatin	158±6.0	176,20±12.6	182.8±11.4	11.5±10.5 (a) 3.7±2.1 (b)	0.059 (c) 0.012 (d)	0,636 (f) 0,727 (g)
COC+HFD+ Fenofibrate	171.8±22.9	184.20±14.7	189.4±17.1	7.2±13.3 (a) 2.8±2.6 (b)	0.192 (c) 0.071 (d)	

a= Percentage of change day 0-30; b= Percentage of change day 30-60; c= Paired t-test comparing body weight at day 0 to 30; d= Paired T-test comparing body weight at day 30 to 60, e= One-way ANOVA test of body weight on day

Table 2. shows the effect of statins or fibrate on high-density lipoprotein (HDL) cholesterol level

Treatment	HDL (mg/dL)			% Change±SD	P-Value (Paired T.Test)	P-Value (one-way ANOVA)
	Day 0	Day 30	Day 60			
COC+HFD+ Vehicle	57±3.1	49.4±4.7	50±5.6	-13.3±8.1 (a) 1.2±8.7 (b)	0.030 (c) 0.790 (d)	
COC+HFD+ Simvastatin	56±8.3	53.8±10.1	62.2±11.5	-3.9±17.2 (a) 15.6±25.1 (b)	0.638 (c) 0.231 (d)	0,134 (e)
COC+HFD+ Rosuvastatin	51.4±1.2	50.2±4.6	58±7.3	-2.3±7.2 (a) 15.5±22.3 (b)	0.603 (c) 0.205 (d)	0,528 (f) 0,575 (g)
COC+HFD+ Fenofibrate	49.2±3.9	46.4±9.6	56.8±15.6	-5.6±24.4 (a) 22.4±42.2 (b)	0.644 (c) 0.264 (d)	

a= Percentage of change day 0-30; b= Percentage of change day 30-60; c= Paired t-test comparing HDL levels at day 0 to 30; d= Paired T-test comparing HDL levels at day 30 to 60, e= One-way ANOVA test HDL levels on day 0, f= One way ANOVA test HDL levels on day 30, g= One way ANOVA test the proportion of changes in HDL levels on day 30-60

eight weeks resulted in elevated total cholesterol. The effect on triglyceride/HDL-C, total/HDL-C, and LDL-C/HDL-C depends on the dose of the contraceptive while the effect on TC and LDL was not dose-dependent. Administrations of a low dose of combined oral contraceptive and a high-fat diet may produce a greater cardiovascular risk than administrations of a high dose of combined oral contraceptive and high-fat diet (Jeremiah and Soladoye 2017). In (Xu *et al.* 2014), both simvastatin and fenofibrate could prevent renal damage caused by lipid disorders after four weeks.

Triglyceride Levels of Rats

Estrogen has been claimed to instigate hypertriglyceridemia in postmenopausal women taking oral hormone therapy. This happens due to progestins counteraction against estrogen (Tsimihodimos *et al.* 2005). In Table 3, it can be seen that the administration of contraceptive pills and a high-fat diet for 30 days caused an increase in TG levels in most treatment groups ($P<0.05$). Interestingly, after receiving simvastatin therapy, the TG continued to rise on day 60; yet, this TG elevation did not achieve statistical significance compared to day 30. In contrast, the administration of rosuvastatin and fenofibrate for 30 days prevented the elevation of TG levels on day 60.

Fibrates are commonly referred to as peroxisome proliferator active receptor agonists (PPAR-α). PPAR-α expression is present in the liver, kidney, endothelium, and vascular smooth muscle. They significantly lower triglycerides and increase HDL-C without reducing LDL-C associated with a significant reduction in coronary events. However, statins or fibrates affect various aspects of lipoprotein metabolism. Therefore, it is challenging for statin or fibrate monotherapy to alter the lipid profile of patients with combined hyperlipidemia (Dixit and Jagan 2016).

Statins are 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase inhibitors that effectively lower total and LDL-C (Gheorghe *et al.* 2020). Statins differ in their pharmacokinetic characteristics, partly because of their mode of administration and partly because of their lipophilicity. Simvastatin is given as an inactive form of lactone converted to an active form in the body. On the other hand, rosuvastatin is shown in the form of an active acid. Hydrophilic statins require carrier-mediated uptake into the liver, whereas lipophilic statins can diffuse passively through cell membranes which decreases their hepatoselectivity because they can also diffuse into other tissues. Lipophilic statins are generally cleared by oxidative biotransformation, whereas hydrophilic statins are excreted unchanged. Metabolism occurs mainly via CYP3A4 to simvastatin, whereas rosuvastatin is principally metabolized via CYP2C9. In addition, all statins are substrates of several membrane transporters (Ward *et al.* 2019).

Rosuvastatin competitively inhibits the enzyme HMG-CoA reductase selectively and reversibly. This enzyme converts HMG-CoA to mevalonic acid in the cholesterol biosynthetic pathway, which is a rate-limiting step in cholesterol synthesis. Therefore, rosuvastatin decreases hepatic sterol synthesis, leading to a decrease in hepatocellular cholesterol concentration. Rosuvastatin has shown a reduction in TG concentrations compared to other statins, with the most significant benefit seen in patients with high baseline TG levels. Rosuvastatin increases HDL-C by

Table 3. The effect of statins or fibrate therapies on triglyceride levels

Treatment	TG (mg/dL)			% Change±SD	P-Value (Paired T.Test)	P-Value (one way ANOVA)
	(Day 0)	(Day 30)	(Day 60)			
COC+HFD+ Vehicle	27.8±11.9	77.2±41.2	75.8±36.4	177.7±84.4 (a) 1.8±33.5 (b)	0.025 (c) 0.867 (d)	0,004 (e) 0,319 (f) 0,483 (g)
COC+HFD+ Simvastatin	47±11.1	74±21.5	97.4±21.6	57.4±84.3 (a) 31.6±45.4 (b)	0.115 (c) 0.093 (d)	
COC+HFD+ Rosuvastatin	40.4±6.1	66.4±21.6	64.6±15.6	64.3±68.6 (a) -2.7±39.1 (b)	0.079 (c) 0.887 (d)	
COC+HFD+ Fenofibrate	24.8±5.2	47.4±13.6	48.8±17.5	91.1±77.9 (a) 2.9±45.3 (b)	0.042 (c) 0.885 (d)	

a= Percentage of change day 0-30; b= Percentage of change day 30-60; c= Paired t-test comparing body TG levels on day 0 and 30; d= Paired T-test comparing TG levels at day 30 to 60, e= One-way ANOVA test TG levels on day 0, f= One way ANOVA test TG levels on day 30, g= One way ANOVA test the proportion of changes TG levels on day 30-60

Table 4. Represents the average total cholesterol (TC) level before and after the treatments

Treatment	TC (mg/dL)			% Change±SD	P-Value (Paired T.Test)	P-Value (one way ANOVA)
	(Day 0)	(Day 30)	(Day 60)			
COC+HFD+ Vehicle	922.±13.1	131.6±36.1	128.8±34.7	42.7±26.3 (a)[a] -2.1±17.1 (b)	0.034 (c) 0.767 (d)	0,013 (e) 0,122 (f) 0,322 (g)
COC+HFD+ Simvastatin	109.4±18.9	131.6±19.1	163.8±35.2	20.2±40.2 (a) 24.4±15.5 (b)	0.253 (c) 0.038 (d)	
COC+HFD+ Rosuvastatin	97.4±9.9	120.8±24.8	127.8±16	24±34.9 (a) 5.7±29.2 (b)	0.169 (c) 0.682 (d)	
COC+HFD+ Fenofibrate	78.4±6.2	95±19.1	110±19.1	21.1±30 (a) 16.6±22.8 (b)	0.155 (c) 0.139 (d)	

a= Percentage of change day 0-30; b= Percentage of change day 30-60; c= Paired t-test comparing TC levels at day 0 to 30; d= Paired T-test comparing TC levels at day 30 to 60, e= One-way ANOVA test TC levels on day 0, f= One way ANOVA test TC levels on day 30, g= One way ANOVA test the proportion of changes TC levels on day 30-60

8%-12% with no clear relationship between dose and response, although the increase is most significant in patients with low baseline HDL-C levels (Luvai *et al.* 2012).

However, in this study, we found a significant difference in decreasing TG but not in increasing HDL. This may be due to the different mechanisms of hyperlipidemia induction using the combined contraceptive pill.

Total Cholesterol Levels of Rats

Plasma cholesterol levels can be increased by a high intake of saturated fat since it increases the fatty deposits in the liver which is then converted to cholesterol. This effect can be exacerbating in women using a hormonal contraception for a long period. Although estrogen may halt lipid metabolism, progesterone effect can increase liver lipase activity leading to lipid melabolism dysfunction (Aasare *et al*. 2014). In this study 30 days of contraceptive pills and a high-fat diet administration caused elevation of TC levels in each treatment group and achieved a significant difference in the placebo group (Table 4). Following the administration of therapies, TC continued to rise, especially in the simvastatin and fenofibrate groups. Meanwhile, the TC level of rosuvastatin only slightly increased (~5.7%).

Fibrates are another group of hypolipidemic drugs that regulate lipid metabolism. Fibrates function to reduce high TG levels and increase HDL-C levels, which are characteristic lipid disorders commonly seen in patients with diabetes or metabolic syndrome (Chen *et al.* 2013). Meanwhile, statins lower plasma LDL-C by competitively inhibiting the enzyme HMG-CoA reductase in the liver, which is a rate-limiting enzyme in the cholesterol biosynthetic pathway. As a result, the conversion of HMG-CoA to mevalonate is inhibited, leading to a resultant reduction in cholesterol (Dixit and Jagan 2016). However, in animal models with contraceptive pill induction, fibrates did not decrease TG and TC and did not increase the HDL levels in rats.

The pharmacokinetics of each statin is based on its hydrophobic properties. For lipophilic statins (lovastatin, simvastatin, fluvastatin, and atorvastatin), transport is done by passive diffusion and is well metabolized by CYP enzymes. The main route of excretion is through the biliary system. Meanwhile, for the more hydrophilic statins such as rosuvastatin and pravastatin, active transport is the primary mode of entry into the liver. They are metabolized less by CYP enzymes and are actively excreted via the kidneys. Lipophilic statins show an efficient activity in both hepatic and extrahepatic sites while hydrophilic statins are more hepatoselective. Lipophilic statins have the general property of low bioavailability due to the first-pass metabolism (Shuhaili *et al.* 2017). This study shows that the hydrophilic statin rosuvastatin has a better effect than simvastatin, a lipophilic statin.

This study has several limitations. First, the composition of the high-fat diet in this study only relied on duck egg yolks to cause dyslipidemia. This might be inadequate to trigger lipid disorder after 60 days of treatment. Previously, a preclinical study showed that 60 days of a high-fat diet in rats was sufficient to cause metabolic acidosis and lipid disorder in rats using a combination of goat fat and egg yolks (Arsyad *et al.* 2020). Second, a lack of preliminary study regarding the therapeutic doses for rats could also be a confounding factor. Third, the current study had a limited number of samples, which were only five animals per group which consequently costed a lack of statistical power and made it challenging to achieve statistical significance.

CONCLUSION

It was concluded that among the treatments, fenofibrate was more effective in reducing weight gain and slightly improving the lipid profile of dyslipidemic rats induced by oral contraception and a high-fat diet. However, when comparing all the treatment groups, there was no significant difference found in the rats' body weight, TC, TG, and HDL levels after 60 days.

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