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ARTICLE



Ameliorating Effects of Four-Week Fiber-Multivitamin Combination Treatment on Low-Density Lipoprotein Cholesterol, Total Cholesterol, and Apolipoprotein B Profiles in Hypercholesterolemic Participants

Kusnandar Anggadiredja, MSc, PhD^a, Nazhifa Ufamy, MD, MSc^{a,b},
Lia Amalia, MSc, PhD^a, Neng Fisheri Kurniati, MSc, PhD^a, and
Irianti Bahana Maulida Reyaan, MSc^a

^aDepartment of Pharmacology and Clinical Pharmacy, School of Pharmacy, Institut Teknologi Bandung (ITB), Bandung, Indonesia; ^bFaculty of Medicine, Jenderal Achmad Yani University, Bandung, Indonesia

ABSTRACT

Hyperlipidemia is one of the leading causes of death and requires lipid-lowering treatment to reduce morbidity and mortality. Effective and safe alternative and adjunctive therapies could be beneficial for patients with hyperlipidemia. To assess the effect of a fiber-multivitamin combination product on the lipid parameters low-density lipoprotein cholesterol (LDL-c), high-density lipoprotein cholesterol (HDL-c), total cholesterol (TC), triglyceride (TG), and apolipoprotein B (Apo B) in patients with hypercholesterolemia, we conducted a double-blind, randomized, parallel-group study. Forty-one out of 50 randomized hypercholesterolemic participants recruited between August 2016 and March 2018 completed the trial. The participants were assigned to receive either test product (treatment group, $n = 20$) or placebo (placebo group, $n = 21$) for 4 weeks following a 6-week dietary intervention (based on education from a dietitian) run-in period. The primary outcome was LDL-c levels and the secondary outcomes were HDL-c, TC, TG, and Apo B levels. All of the outcomes were measured at baseline and week 4 after the completion of run-in period. Participants in both groups had similar LDL-c levels (142 ± 15.7 vs. 143 ± 19.3 mg/dL). After 4 weeks of exposure to test product, participants in the treatment group demonstrated a 17.25 ± 22.26 reduction in LDL-c ($p < .05$ vs. placebo). This improvement in LDL-c was accompanied by amelioration in TC and Apo B levels, without any detrimental effects on HDL and TG concentration. Results of the present study suggest that fiber-vitamin combination has potential to be used as an adjunct therapy for the management of hypercholesterolemia.

KEYWORDS

ameliorating effects; fiber; hypercholesterolemia; LDL-c; multivitamin

Introduction

Diseases related to elevated levels of blood lipids are one of the leading causes of death. The World Health Organization (WHO) has reported that the prevalence of elevated total cholesterol was highest in Europe (54% for both sexes), followed by America (48%

CONTACT Kusnandar Anggadiredja ✉ kusnandar@fa.itb.ac.id Department of Pharmacology and Clinical Pharmacy, School of Pharmacy ITB, Gedung Yusuf Panigoro (Labtek VII), Jl. Ganesa 10, Bandung 40132, Indonesia.

for both sexes). Africa and Southeast Asia showed the lowest percentages (22.6% and 29.0%, respectively).

Dietary supplementation has been subjected to research as a mode of adjunct therapy for hyperlipidemia (Cicero et al. 2012; Pirro et al. 2017). Phytosterols and soluble fibers have been particularly demonstrated to lower blood lipid. In addition, inclusion of other nutrients, including vitamins, has also been indicated to improve blood lipid profiles (Cicero et al. 2017).

The use of a product containing fiber and multivitamins has been reported to be a potential adjunct therapy for lowering blood lipid levels. In addition, previous studies (Sprecher and Pearce 2002; Verdegem 2007) have shown a product containing fiber and vitamins decreased the levels of low-density lipoprotein (LDL) concentration, with other promising additional benefits such as decreasing homocysteine and triglyceride levels.

In our study, we investigated the effects of a fiber-multivitamin combination product on lipid profiles in hypercholesterolemic patients. This study is the first controlled study to assess the effects of the product using Indonesian participants.

Methods

Study design

We randomized hypercholesterolemic participants in a double-blind, randomized, parallel-designed trial comparing the effects of a four-week exposure of test product on lipid parameter, with LDL cholesterol (LDL-c) level as the primary measure versus placebo. The study was conducted between September 2016 and March 2018. The study was approved by the Institutional Review Board of Hasan Sadikin General Hospital Bandung, Indonesia (LB.04.01/A05/EC/297/IX/2016).

Study participants

The criteria of inclusion for the potential study participants were ≥ 18 years of age, a fasting LDL-c concentration of ≥ 130 mg/dL at two points of measurement before randomization, and naïve to lipid-lowering therapy or statins. Participants were required to follow the dietitian's advice delivered in a counseling session for the diet during the course of investigation. Participants were not eligible for study if they had LDL-c level of less than 130 mg/dL after the six-week run-in period in which they were subject to diet scheme as advised by the counseled dietitian. In addition, participants whose LDL-c concentration did not stabilize (within 15% variance) in the period from three to six weeks before randomization were also excluded. Pregnant and breast-feeding participants were excluded. Participants were also excluded if they had established thyroid/liver/renal disease, diabetes mellitus (fasting glucose ≥ 200 mg/dl), vasculitis, HIV infection, dysphagia/swallowing disorder, hypertension (systolic blood pressure [BP] ≥ 140 , diastolic BP ≥ 90 mmHg), known cardiovascular/unstable cardiac disease, or allergy to ingredients of test product or placebo. All participants provided informed consent to participate in this investigation, which was approved by the Institutional Review Board of Hasan Sadikin General Hospital Bandung, Indonesia. Participants were compensated for their participation in the trial upon completion of the experiments.

Study interventions

Participants who remained eligible for the trial after the six-week dietary intervention run-in were randomized ($n = 41$) to receive either placebo or test product (treatment) in a double-blind parallel fashion. The randomized participants continued to follow the diet scheme for the next four weeks with the addition of two servings per day of their assigned study compound, after they signed informed consent forms. The test product was Bios-Life C (Unicity International, Orem, UT), which provided 4.0 g of soluble fiber and 0.5 g of insoluble fiber per serving (guar gum, locust bean gum, pectin, oat fiber, gum acacia, and barley fiber), along with 1,000 IU vitamin A as β carotene, 30 IU vitamin E, 60 mg vitamin C, 2.7 mg thiamin, 36 mg niacin, 3.1 mg riboflavin, 120 μ g folic acid, 3.6 mg vitamin B6, 9 μ g vitamin B12, 30 μ g biotin, 100 mg calcium, 0.9 mg zinc, 54 μ g chromium, and 4.2 μ g selenium. The placebo consisted entirely of insoluble fiber, provided as a combination of resistant maltodextrin, carboxymethylcellulose, and beta carotene (Unicity International, Orem, UT). These powders were of identical appearance, color, odor, and flavor. Both products were dispensed as identical single-serving packets of powder to be mixed with 200 ml of water and consumed within 30 minutes of a meal, twice per day. The participants attended the clinic four weeks after randomization. A lipid panel, including total cholesterol (TC), LDL-c, high-density lipoprotein cholesterol (HDL-c), triglyceride (TG), and cardiovascular risk ratio, was measured at baseline (BL) and week 4 after completion of the run-in period. The cholesterol measurements were performed on-site using Dimension Clinical Chemistry System (Siemens, Marburg, Germany). In addition, all participants were assessed for apolipoprotein B (Apo B) concentration. Participants were instructed to come in fasted (having no foods or drinks other than water since going to bed the previous night) before each measuring day. Compliance with the protocol was assessed by a weekly phone call with all participants, during which evaluation of adverse effects was also carried out.

Randomization

The research coordinator randomly assigned eligible participants to either test product or placebo group in a 1:1 randomization scheme. Study investigators and research coordinators were blinded to treatment allocation.

Study outcome

The primary outcome was LDL-c level, and as secondary outcomes we recorded the levels of HDL-c, TC, TG, and Apo-B. All of the outcomes were measured at baseline and week 4 after the completion of the run-in period.

Sample size and statistical analysis

Calculation of sample size was based on anticipated means of LDL-c levels of treatment and placebo group, which were 120 and 140, respectively; alpha value of .05; and power set at 90%. With this setting, we obtained a respective minimum sample size of 8. Experimental data are represented as mean \pm standard error of the mean (SEM).

Within-group differences over time were analyzed using paired *t* tests for all parameters measured, while between-group differences at each observation point were assessed by unpaired *t* test. Statistical significance was defined at $p \leq .05$.

Results

Study population

A total of 134 candidates were screened for eligibility, and 50 participants met the criteria of eligibility, which were then randomized between September 2016 and March 2018. Out of 50 participants randomized, 41 (20 treatment, 21 placebo) completed the four-week protocol. Reason for discontinuation of the nine participants (5 treatment, 4 placebo) was the lack of further interest in participation because they thought the regimen was too long. Demographic data of the 41 participants who completed the study are presented in Table 1.

LDL-c response

LDL-c concentrations in treatment and placebo groups were virtually identical after the six-week diet lead-in (142 ± 15.7 vs. 143 ± 19.3 mg/dL). At the end of the four-week randomization period, as shown in Figure 1, LDL-c level in the treatment group was significantly lower compared to placebo (125.15 ± 4.86 vs. 142.90 ± 5.19 mg/dL, $p = 0.024$). LDL-c response at the end of the trial was, therefore, -17.25 ± 22.26 for the treatment group compared to 0.00 ± 20.00 for the placebo group ($p = .013$). In all, 25% ($n = 5$) of treatment participants experienced an LDL reduction of greater than 20% compared to 4.8% ($n = 1$) in the placebo group.

HDL-c concentration

As shown in Figure 2, HDL-c concentrations were not significantly different in treatment and placebo groups either at prerandomization or at the end of the study (57.30 ± 2.90 vs. 52.85 ± 2.26 , $p > .05$ and 56.55 ± 3.03 vs. 55.24 ± 1.95 , $p > .05$).

Table 1. Demographic data of participants who completed the study.

	Bios-Life C	Placebo	<i>p</i> value
<i>n</i>	20	21	–
Age (yr)	42 ± 11.7	38.6 ± 3.9	.36
Female	90%	81%	.66
LDL-c (mg/dl)	142 ± 15.7	143 ± 19.3	.93
TC (mg/dl)	213.9 ± 22.8	212.1 ± 28	.82
HDL-c (mg/dl)	57.3 ± 12.9	52.9 ± 10.4	.23
TG (mg/dl)	104.9 ± 44.5	114 ± 58	.58
LDL-c:HDL-c	2.6 ± 0.6	2.8 ± 0.6	.29
BMI (kg/m ²)	26.9 ± 4.3	25.5 ± 3.8	.28
Systolic BP (mmHg)	113.4 ± 9.7	106.3 ± 12.1	.21
Diastolic BP (mmHg)	77.4 ± 7.3	71.8 ± 9.9	.11

LDL-c = low-density lipoprotein cholesterol; TC = total cholesterol; HDL-c = high-density lipoprotein cholesterol; TG = triglycerides; BMI = body mass index; BP = blood pressure.

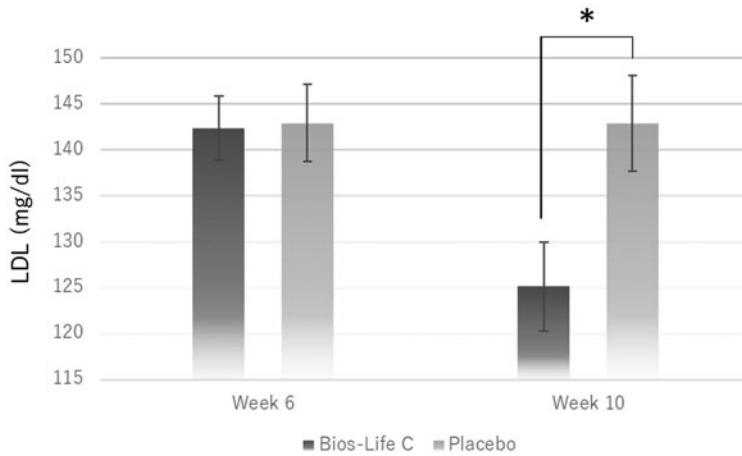


Figure 1. Effects of administration of fiber-multivitamin combination product on LDL-c levels. Prior to randomization, participants underwent a 6-week dietary intervention run-in period. Participants received the test product or placebo twice daily for 4 weeks. Data represent averages \pm standard error of the mean (SEM) of 20 and 21 participants in Treatment and Placebo groups, respectively. LDL-c = low-density lipoprotein cholesterol. * $p < .05$, unpaired t test.

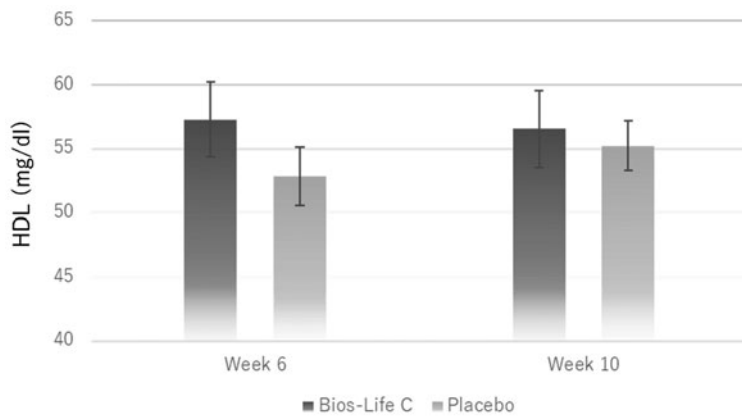


Figure 2. Effects of administration of fiber-multivitamin combination product on HDL-c levels. Prior to randomization participants underwent a 6-week dietary intervention run-in period. Participants received the test product or placebo twice daily for 4 weeks. Data represent averages \pm standard error of the mean (SEM) of 20 and 21 participants in Treatment and Placebo groups, respectively. HDL-c = high-density lipoprotein cholesterol. * $p < .05$, unpaired t test.

LDL:HDL ratio

Figure 3 depicts the data on LDL:HDL ratio. The ratio decreased by $10.26\% \pm 15.46\%$ in the treatment group ($p = .007$) but did not change significantly ($4.22\% \pm 13.43\%$, $p > .05$) in the placebo group.

TC concentration

Figure 4 demonstrates that while TC concentrations in treatment and placebo groups were not significantly different at prerandomization of week 6 (213.90 ± 5.091 vs. 212.10 ± 6.11 ,

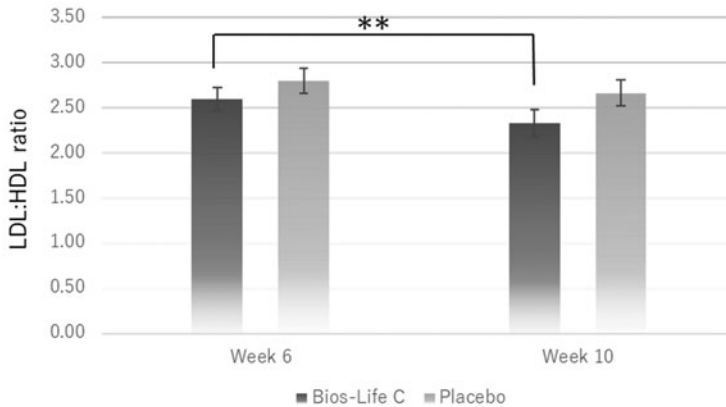


Figure 3. Effects of administration of fiber-multivitamin combination product on LDL-c:HDL-c ratio. Prior to randomization, participants underwent a 6-week dietary intervention run-in period. Participants received the test product or placebo twice daily for 4 weeks. Data represent averages \pm standard error of the mean (SEM) of 20 and 21 participants in Treatment and Placebo groups, respectively. In total, (average) decreases in LDL-c:HDL-c ratio were $10.26\% \pm 15.46\%$ and $4.22\% \pm 13.43\%$ in test product and Placebo, respectively. LDL-c = low-density lipoprotein cholesterol; HDL-c = high-density lipoprotein cholesterol. $**p < .01$, paired *t* test.

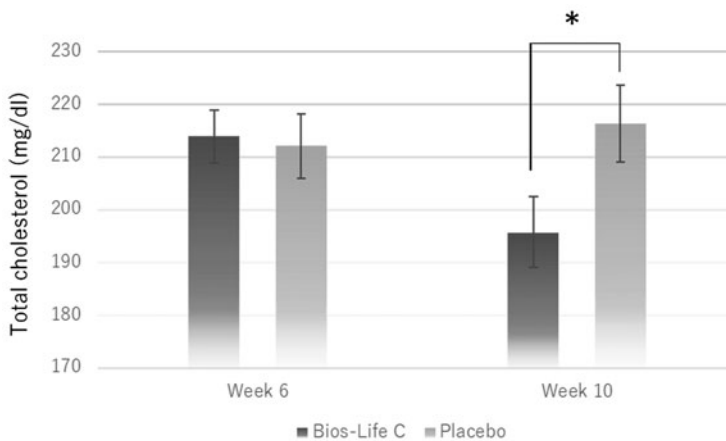


Figure 4. Effects of administration of fiber-multivitamin combination product on total cholesterol (TC) levels. Prior to randomization, participants underwent a 6-week dietary intervention run-in period. Participants received the test product or placebo twice daily for 4 weeks. Data represent averages \pm standard error of the mean (SEM) of 20 and 21 participants in Treatment and Placebo groups, respectively. $*p < .05$, unpaired *t* test.

$p > .05$), the concentration in the treatment group was significantly lower than in the placebo group at the end of the trial (195.75 ± 6.68 vs. 216.43 ± 7.34 , $p = .04$).

TG concentration

As shown in Figure 5, with regard to TG concentration, there was no significant difference found between treatment and placebo groups either at prerandomization or at the end of the study (104.90 ± 9.94 vs. 113.95 ± 12.65 , $p > .05$ and 96.20 ± 9.99 vs. 102.4 ± 11.95 , $p > .05$).

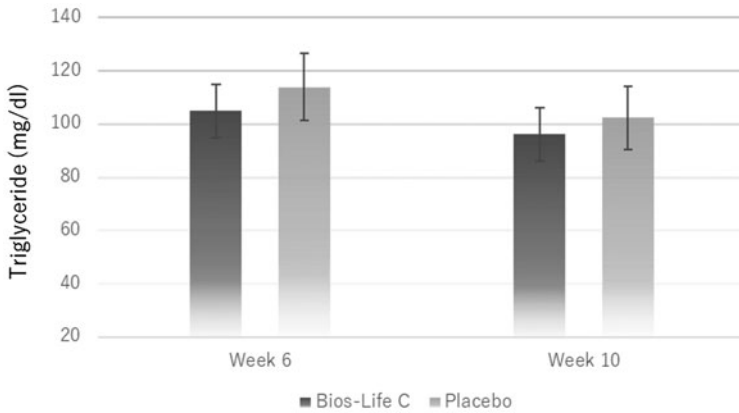


Figure 5. Effects of administration of fiber-multivitamin combination product on triglyceride (TG) levels. Prior to randomization, participants underwent a 6-week dietary intervention run-in period. Participants received the test product or placebo twice daily for 4 weeks. Data represent averages \pm standard error of the mean (SEM) of 20 and 21 participants in Treatment and Placebo groups, respectively. * $p < .05$, unpaired t test.

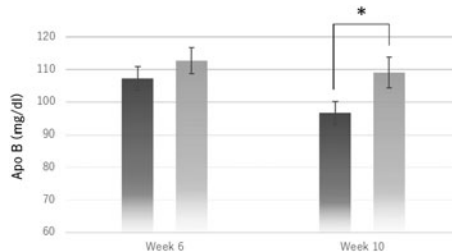


Figure 6. Effects of administration of fiber-multivitamin combination product on apolipoprotein B (Apo-B) levels. Prior to randomization, participants underwent a 6-week dietary intervention run-in period. Participants received the test product or placebo twice daily for 4 weeks. Data represent averages \pm standard error of the mean (SEM) of 20 and 21 participants in Treatment and Placebo groups, respectively. * $p < .05$, unpaired t test.

Apo B concentration

Results on the measurement of Apo B concentration are presented in Figure 6. No significant difference was observed in this parameter at prerandomization of week 6 (107.25 ± 3.65 vs. 112.76 ± 4.02 , $p > .05$). At the end of the trial, however, the concentration was significantly lower ($p = .04$) in the treatment group (96.7 ± 3.47) compared to placebo (109.10 ± 4.78).

Reported adverse effects and death

Upset stomach and flatulence were the major adverse effects reported by participants who completed the trial in both groups. In treatment and placebo group, upset stomach was reported by 2 (10%) and 1 (4.8%) participants, respectively. Meanwhile, the respective numbers of participants complaining of flatulence were 2 (10%) and 2 (9.5%). All adverse effects were manageable and did not lead to withdrawal from the trial. No death occurred during this trial.

Discussion

In the present double-blind randomized trial, we found that a high-soluble-fiber mixture, supplemented with a full complement of vitamins, reduced LDL-c, as the primary indicator, by 17.25% compared to placebo. This result was demonstrated without detrimental effect on HDL-c or TG concentrations. Significant improvements were also observed in LDL:HDL ratio and Apo B levels. These characteristics could make the test product an important part of the preventive armamentarium against hyperlipidemia, in a nonsystemic way.

While it was observed to be relatively constant in the treatment group, HDL-c level was seen to have an increasing trend in participants treated with placebo. This is likely a result of the higher level, albeit not significant, of baseline HDL in the treatment group compared to placebo. The hypothesis is corroborated by the observation that most participants in the placebo group having baseline HDL-c of lower than 50 mg/dL had highest increase in HDL-c level (two participants showed 16- and 20-unit increase, respectively). Early data showed that diet is an important modifier of LDL-c concentration. Thus, a diet containing low carbohydrate and high protein has been reported to improve blood HDL-c profile (Wilson and Lees 1972; Thorning et al. 2015), and the same is true for a similar diet scheme combined with exercise (Ramírez-Vélez et al. 2018). It is, therefore, comprehensible to expect HDL increase in participants of the present study who strictly followed the diet scheme as educated prior to the six-week run-in period. The reason for the unchanged level of HDL-c in the treatment group is uncertain, but two previous studies (Sprecher and Pearce 2002; Verdegem 2007) using similar test product showed that significant changes were not found when the parameter was checked at week 4 of administration. Overall, no deleterious effects whatsoever were observed on HDL-c concentration following consumption of the test product.

A meta-analysis from eight control trials indicated a 7% average reduction in LDL-c, along with subtle 1%–3% increases in TG and decreases in HDL-c (Anderson et al. 2000). Meanwhile, guar gum/pectin combination therapy resulted in 7% to 8% reductions in LDL, with LDL-c:HDL-c ratio reductions of 6%–9% (Hunninghake et al. 1994) and no clear change in HDL-c or TG. While this pattern is consistent with the present result, we observed more than 10% reduction in the LDL-c: HDL-c ratio. Another meta-analysis (Wei et al. 2009) further demonstrated dose and time dependency of psyllium effect, which is not only consistent with our results but also provides the basis to expect a better outcome from our study when the study was extended.

Apo B is an important lipoprotein component of many of the most atherogenic lipoprotein particles. An early study (Lamarche et al. 1996) has shown that apo B may be a better predictor of cardiovascular disease risk than LDL-c. Furthermore, it has been shown that apo B may be elevated despite normal or low concentrations of LDL-c. Apo B also appears to predict on-treatment risk when LDL-c has been lowered by statin therapy (Walldius et al. 2001). The INTERHEART study found that the apo B/apo A1 ratio is more effective at predicting heart attack risk than either the apo B or apo A1 measure alone (Yusuf et al. 2004). Our present results showing Apo B-lowering effect of the test product provides the strong basis for the use of this fiber-multivitamin combination in hypercholesterolemic individuals.

The safety profile of the test product was found to be consistent, with gastrointestinal consequences as the major adverse effect reported by the participants. The effects reported were in line with previous studies testing fiber supplementation (Sprecher and Pearce, 2002), which were manageable and did not result in severe consequences and participant withdrawal from the trial.

Conclusion

The fiber and multivitamin combination is a promising natural dietary intervention to lower LDL cholesterol and total cholesterol and at the same time reduce Apo B levels while simultaneously increasing HDL cholesterol. Consistent with previous similar studies, the changes observed in LDL-c for participants with “borderline high” and “high” cholesterol levels may be comparable to the effects of statin medication, with manageable adverse effects. This study, however, warrants further assessment using a larger number of participants with follow-up period and better compliance.

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Notes

1. Department of Pharmacology and Clinical Pharmacy, School of Pharmacy, Institut Teknologi Bandung (ITB), Bandung, Indonesia.
2. Faculty of Medicine, Jenderal Achmad Yani University, Bandung, Indonesia.
3. Cardiology and Vascular Medicine Department, Faculty of Medicine, Padjadjaran University, Bandung, Indonesia.
4. Integrated Cardiology Service Department, Hasan Sadikin General Hospital, Bandung, Indonesia.
5. Clinical Nutrition Department, Hasan Sadikin General Hospital, Bandung, Indonesia.
6. Clinical Pathology Department, Hasan Sadikin General Hospital, Bandung, Indonesia.

Declaration of interest

The authors declare no conflicts of interest. The authors alone are responsible for the content and writing of the article.

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About the authors

Kusnandar Anggadiredja, MSc, PhD, Department of Pharmacology and Clinical Pharmacy, School of Pharmacy, Institut Teknologi Bandung (ITB), Bandung, Indonesia. Research interests are KA: Neuropharmacology, LA: Clinical and community pharmacy, NFK: Pharmacology of the cardiovascular and endocrine systems, IBMR: Clinical and community pharmacy.

Nazhifa Ufamy, MD, MSc, Faculty of Medicine, Jenderal Achmad Yani University, Bandung, Indonesia. Research interest is Community health.

Lia Amalia, MSc, PhD, Department of Pharmacology and Clinical Pharmacy, School of Pharmacy, Institut Teknologi Bandung (ITB), Bandung, Indonesia. Research interests are KA: Neuropharmacology, LA: Clinical and community pharmacy, NFK: Pharmacology of the cardiovascular and endocrine systems, IBMR: Clinical and community pharmacy.

Neng Fisher Kurniati, MSc, PhD, Department of Pharmacology and Clinical Pharmacy, School of Pharmacy, Institut Teknologi Bandung (ITB), Bandung, Indonesia. Research interests are KA: Neuropharmacology, LA: Clinical and community pharmacy, NFK: Pharmacology of the cardiovascular and endocrine systems, IBMR: Clinical and community pharmacy.

Irianti Bahana Maulida Reyaan, MSc, Department of Pharmacology and Clinical Pharmacy, School of Pharmacy, Institut Teknologi Bandung (ITB), Bandung, Indonesia. Research interests are KA: Neuropharmacology, LA: Clinical and community pharmacy, NFK: Pharmacology of the cardiovascular and endocrine systems, IBMR: Clinical and community pharmacy

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