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Effect of Perilla Oil on Reducing Arteriosclerosis Risk: A Randomized Controlled Cross-Over Study

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Abstract

The risk of arteriosclerosis may be reduced by increasing the levels of α-linolenic acid (ALA), a omega-3 polyunsaturated fatty acid. Perilla oil contains abundant ALA. This randomized crossover clinical study of perilla oil investigated its safety and effects on the levels of ALA and lipid profile in 10 subjects. Half of the subjects took 1 tablespoon of perilla oil (ALA content = approximately 9.4 g) and the remaining half took 1 tablespoon of olive oil (ALA content = approximately 0.09 g) daily for 1 week. After a 28-day washout period, each group switched and took the other oil for 1 week. Variables were measured before and after each week of oil ingestion. The ratio of low density lipoprotein cholesterol to high density lipoprotein cholesterol significantly decreased after ingestion of perilla oil (2.7 ± 0.6 vs. 2.6 ± 0.6, $P = 0.037$). The levels of ALA significantly increased after ingestion of perilla oil (31.6 ± 10.32 vs. 67.93 ± 24.35 μg/mL, $P = 0.001$). There were no adverse effects related to perilla oil. Therefore, as a dietary supplement, perilla oil has beneficial effects on the levels of ALA and lipid profile, suggesting that it contributes to a reduction in the risk of arteriosclerosis.

Keywords: *Perilla oil, Olive oil, Arteriosclerosis, Vascular endothelial function, Reactive hyperemia index*

Introduction

Arteriosclerosis leads to heart and cerebrovascular diseases and is the leading cause of death worldwide. Risk factors for arteriosclerosis are diabetes (DM), hypertension, dyslipidemia, obesity, and smoking [1]. Omega - 3 polyunsaturated fatty acids have attracted attention for their prophylactic effect against various disorders, including atherosclerosis, coronary artery disease, and inflammatory diseases [2, 3]. There are reports indicating that a high intake of α-linolenic acid (ALA), a plant-derived omega - 3 polyunsaturated fatty acid, is associated with a reduced risk of arteriosclerosis [4, 5]. Perilla oil contains 50%–60% of ALA. This oil can easily be used as a daily dietary supplement. In the human body, ALA synthesizes eicosapentaenoic acid (EPA) [6]. It has been reported that EPA and docosahexaenoic acid (DHA), both omega - 3 polyunsaturated fatty acids contained in fish oil, exhibit antithrombotic and lipid-lowering actions [7, 8]. There have been few studies of perilla oil and its hypothetical effect on reducing arteriosclerosis.

ALA inhibits arteriosclerosis-associated inflammation and reduces oxidative stress, which contributes to improve vascular endothelial function [9, 10]. Reactive hyperemia index (RHI) has been reported to be useful for evaluating vascular endothelial function. Moreover, it is a good predictor of cardiovascular disease [11, 12]. Previous studies have suggested that ALA reduces diastolic blood pressure and increase serum triacylglycerol concentration [13]. Salonen, J.T et al. showed that estimated dietary intake of linolenic acid has an inverse correlation with mean resting blood pressure [14]. However, it must be noted that overdoses of ALA, EPA, and DHA may cause blood coagulation [15].

We conducted a randomized crossover clinical trial of perilla oil to evaluate its safety and effects on the levels of ALA, lipid profile and endothelial function as markers of atherosclerotic risk.

Materials and Methods

Test diets. Perilla oil, extracted from perilla seeds, was used as the study oil. A commercially available olive oil was used as a placebo control. The ALA content of the perilla oil was 62.9 g/100 g, while that of the olive oil was 0.6 g/100 g. The ALA content was measured at the Japan Food Research Laboratories (Tokyo, Japan). Both oils were given in a dose size of 1 tablespoon as a daily supplement at breakfast for 1 week. The estimated content of ALA in each dose was approximately 9.4 g in the perilla oil and 0.09 g in the olive oil.

Subjects. Ten untreated individuals (4 male and 6 female) who had at least two risk factors for arteriosclerosis (aging, first-degree hypertension, dyslipidemia, DM, obesity, and smoking) were enrolled

[16]. For the purposes of this study, hypertension was defined as a systolic blood pressure of 140 to 159 mmHg or a diastolic blood pressure of 90 to 99 mmHg. Dyslipidemia was defined as a low-density lipoprotein cholesterol (LDL-C) ≧ 140 mg/dL. Diabetes was defined as a fasting blood glucose concentration ≧ 126 mg/dL, or a hemoglobin A1c (HbA1c) ≧ 6.37%. Obesity was defined as a body mass index (BMI) ≧ 25 kg/m^2. Smoking was recorded as a risk factor regardless of whether it was past or present. The definition of aging was 45 years or older men and postmenopausal women. Table 1 shows the subjects' characteristics. The study was approved by the Ethics Committee of Nanpuh Hospital, Kagoshima Kyosaikai, Public Interest Inc. Association, Japan. Clinical examinations were performed according to the principles of the Declaration of Helsinki. Written informed consent was obtained from all individuals.

Table 1. Characteristics of subjects taking perilla oil or olive oil supplements

No	Age	Sex	hyperten-sion	dyslipid-emia	diabetes	obesity	Smok-ing
1	55	Male	No	Yes	No	No	No
2	56	Female	No	Yes	No	No	No
3	44	Male	No	Yes	No	No	Yes
4	57	Female	Yes	Yes	No	No	No
5	59	Female	No	Yes	No	No	No
6	47	Male	No	No	No	Yes	Yes
7	50	Female	Yes	Yes	No	No	No
8	56	Female	No	No	No	Yes	No
9	42	Male	Yes	Yes	No	Yes	Yes
10	56	Female	Yes	Yes	No	Yes	No

Study design. This study was designed as a crossover method. The 10 subjects were randomly divided into two groups of 5, the first group took perilla oil daily for 1 week and the second group took olive oil. After a 28-day washout period, the groups were reversed, with the first group took olive oil daily for 1 week and the second group took perilla oil (Table 2).

Table 2. Protocol of clinical study design

	1st period			WO [3] term	2nd period		
	Day 1	Day 2–7	Day 8	Day 9–35	Day 36	Day 37–42	Day 43
Examination	●	-	●	-	●	-	●
BMI [1]	●	-	●	-	●	-	●
Blood pressure	●	-	●	-	●	-	●
Blood test	●	-	●	-	●	-	●
RHI [2]	●	-	●	-	●	-	●
Intake	●	●	-	-	●	●	-

[1] Body mass index (kg/m^2), [2] Reactive hyperemia index (-), [3] Washout

Variables were measured before and after each 1-week period of oil ingestion. All measurements at the beginning of each period were completed on the first day of the period before the supplement was given. The measurements after each period were taken the next day of the last oil supplement.

Physical parameters were measured including blood pressure, BMI, RHI, and blood examinations. RHI, a measure of peripheral endothelial function, was assessed using peripheral arterial tonometry (EndoPAT 2000; Itamar Medical, Caesarea, Israel) according to the manufacturer's instructions. Serum levels of aspartate and alanine aminotransferase, total protein, γ-glutamyl transferase, and C-reactive protein were determined by latex agglutination using a BM6050 analyzer (Kyowa-Medex Co., Ltd., Tokyo, Japan). Serum levels of uric acid, blood urea nitrogen, glucose, triglycerides, high density lipoprotein cholesterol (HDL-C), LDL-C, and HbA1c were measured using a BioMajesty JCA-BM6050 analyzer (JEOL Ltd., Tokyo, Japan). The white blood cell (WBC), red blood cell (RBC), and platelet counts were measured with an XE-5000 Hematology Analyzer (Sysmex, Co., Hyogo, Japan). Plasma fatty acids (lauric, myristic, myristoleic, myristoleic, palmitic, palmitoleic, stearic, oleic, linoleic, γ-linolenic, α-linolenic, arachidic, eicosenoic, eicosadienoic, 5–8-11 eicosatrienoic, dihomo-γ-linolenic, arachidonic, eicosapentaenoic, behenic, erucic, docosatetraenoic, docosapentaenoic, lignoceric, docosahexaenoic, and nervonic acids) were measured by SRL Inc (Tokyo, Japan).

Subjects were interviewed regarding their intake of the test oils and any symptoms they experienced during the study.

Statistical analysis. Measured values are expressed as means ± standard deviation. The data were assessed using a paired *t*-test to compare results before and after ingestion of each oil. Data were analyzed using SPSS Version 25 (IBM Co., Armonk, NY, USA). A value of $P < 0.05$ was considered statistically significant.

Results

Physical parameters. There were no significant differences in blood pressure, BMI, or RHI before and after the week-long interventions with perilla oil or olive oil (Table 3).

Table 3. Physical parameters in subjects taking perilla oil or olive oil

	Test oils	Before	After	P-value
Systolic blood pressure (mmHg)	Perilla oil	138.6 ± 17.2	139.4 ± 19.0	0.739
	Olive oil	138.5 ± 12.0	135.5 ± 12.5	0.380
Diastolic blood pressure (mmHg)	Perilla oil	87.7 ± 12.6	85.4 ± 14.0	0.090
	Olive oil	84.8 ± 10.7	84.0 ± 7.9	0.658
Body Mass Index (kg/m^2)	Perilla oil	23.5 ± 2.7	23.6 ± 2.8	0.711
	Olive oil	23.5 ± 2.9	23.4 ± 2.9	0.136
Reactive hyperemia index (-)	Perilla oil	1.59 ± 0.41	1.68 ± 0.50	0.571
	Olive oil	1.57 ± 0.32	1.76 ± 0.58	0.100

Values are presented as mean ± standard deviation; n = 10.

Biochemical markers. After a week of perilla oil, the LDL-C/HDL-C ratio decreased significantly from 2.7 ± 0.6 to 2.6 ± 0.6 (P = 0.037, Fig. 1A). There was no statistically significant difference in the LDL-C / HDL-C ratio after subjects ingested olive oil (2.9 ± 0.8 before vs. 2.8 ± 0.7 after, P = 0.314, Fig. 1B). Perilla oil thus improved the LDL-C / HDL-C ratio.

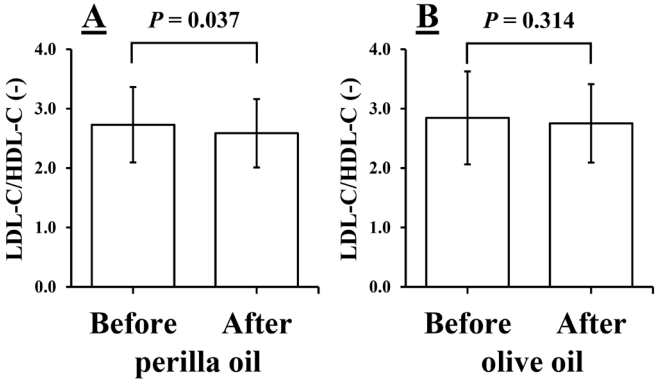

Figure 1. Ratios of low density lipoprotein cholesterol (LDL-C) to high density lipoprotein cholesterol (HDL-C) before and after 1 week of intake of perilla oil (A) or olive oil (B). Values are presented as mean ± standard deviation; n = 10.

With the exception of significant decrease of the platelet count after a week of olive oil, none of the other biochemical or hematologic markers differed significantly before and after either perilla oil or olive oil (Table 4).

Fatty acids. We compared the levels of ALA before and after test oil intake. Fig. 2 shows the result of the levels of ALA before and after 1 week of intake of perilla oil or olive oil, respectively. The levels of ALA increased significantly after intake of perilla oil (31.60 ± 10.32 vs. 67.93 ± 24.35 μg/mL, P = 0.001, Fig. 2A), while the levels did not change after intake of olive oil (30.52 ± 10.34 vs. 32.74 ± 21.26 μg/mL, P = 0.702, Fig. 2B).

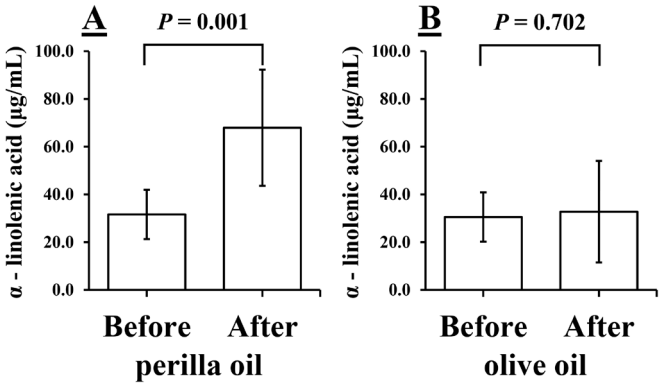

Figure 2. Levels of **α-linolenic acid** before and after 1 week of intake of perilla oil (A) or olive oil (B). Values are presented as mean ± standard deviation; n = 10.

The levels of EPA also increased significantly after perilla oil but not after olive oil (perilla oil: 46.88 ± 16.40 vs. 64.43 ± 31.32 μg/mL, P = 0.023, Fig. 3A; olive oil: 60.44 ± 44.62 vs. 53.90 ± 28.36 μg/mL, P = 0.598, Fig. 3B).

Table 4. Biochemical and hematology markers before and after ingesting perilla oil or olive oil for 1 week

	Group	Before	After	P
Aspartate aminotransferase (IU/L)	Perilla oil	22.0 ± 6.5	24.0 ± 7.2	0.219
	Olive oil	21.6 ± 4.9	22.5 ± 6.2	0.235
Alanine aminotransferase (IU/L)	Perilla oil	26.2 ± 15.4	27.8 ± 15.8	0.437
	Olive oil	26.4 ± 15.8	26.5 ± 17.6	0.968
Total protein (g/dL)	Perilla oil	7.0 ± 0.3	7.0 ± 0.4	0.763
	Olive oil	7.1 ± 0.3	7.0 ± 0. 3	0.273
γ- glutamyl transferase (IU/L)	Perilla oil	42.8 ± 31.1	42.6 ± 30.6	0.937
	Olive oil	48.0 ± 38.5	47.1 ± 38.2	0.780
Uric acid (mg/dL)	Perilla oil	5.6 ± 1.7	5.6 ± 1.6	0.825
	Olive oil	5.8 ± 1.6	5.9 ± 1.5	0.672
Blood urea nitrogen (mg/dL)	Perilla oil	13.3 ± 2.6	12.0 ± 1.6	0.229
	Olive oil	12.6 ± 2.9	13.7 ± 3.6	0.390
Triglyceride (mg/dL)	Perilla oil	129.2 ± 71.8	137.3 ± 70.0	0.585
	Olive oil	122.6 ±59.0	150.9 ± 108.7	0.306
High density lipoprotein cholesterol (HDL-C) (mg/dL)	Perilla oil	64.4 ± 12.8	65.6 ± 14.7	0.549
	Olive oil	64.1 ± 14.0	62.8 ± 12.2	0.593
Low-density lipoprotein cholesterol (LDL-C) (mg/dL)	Perilla oil	171.0 ± 31.5	165.0 ± 30.5	0.400
	Olive oil	174.4 ± 27.7	168.3 ± 32.8	0.147
C-reactive protein (mg/dL)	Perilla oil	0.2 ± 0.2	0.3 ± 0.6	0.569
	Olive oil	0.1 ± 0.1	0.1 ± 0.1	0.835
White blood cell count (10^2/μL)	Perilla oil	55.2 ± 8.3	54.4 ± 10.8	0.741
	Olive oil	53.3 ± 9.7	59.2 ± 6.8	0.050
Red blood cell count (10^4/μL)	Perilla oil	445.5 ± 44.9	444.4 ± 40.0	0.828
	Olive oil	448.4 ± 42.1	446.7 ± 37.6	0.564
Platelet count (10^4/μL)	Perilla oil	26.0 ± 9.8	26.1 ± 10.1	0.628
	Olive oil	27.5 ±10.7	26.3 ± 11.0	0.008*
Blood sugar (mg/dL)	Perilla oil	100.5 ± 10.5	98.5 ± 5.5	0.363
	Olive oil	99.8 ± 9.3	101.1 ± 11.0	0.537
Hemoglobin A1c (%)	Perilla oil	5.4 ± 0.4	5.3 ± 0.4	0.394
	Olive oil	5.3 ± 0.4	5.4 ± 0.4	0.096

Values are presented as mean ± standard deviation; n = 10.
*Significant difference in values analyzed with a paired t-test.

None of the other fatty acids differed significantly before and after intake of either oil (Table 5).

Table 5. Levels of Fatty acid before and after ingestion of perilla oil or olive oil for 1 week

	Group	Before	After	P
Lauric acid (μg/mL)	Perilla oil	1.96 ± 1.21	2.37 ± 1.19	0.156
	Olive oil	2.83 ± 2.18	2.80 ± 1.56	0.974
Myristic acid (μg/mL)	Perilla oil	25.65 ± 11.17	29.55 ± 14.12	0.160
	Olive oil	28.21 ± 10.11	31.96 ± 18.92	0.504
Myristoleic acid (μg/mL)	Perilla oil	1.45 ± 0.68	2.04 ± 1.59	0.147
	Olive oil	1.50 ± 0.62	2.48 ± 2.32	0.223
Myristoleic acid (%)	Perilla oil	0.04 ± 0.02	0.05 ± 0.04	0.153
	Olive oil	0.04 ± 0.01	0.06 ± 0.06	0.283
Palmitic acid (μg/mL)	Perilla oil	806.65 ± 179.01	840.05 ± 199.55	0.271
	Olive oil	817.21 ± 168.76	862.76 ± 261.01	0.522
Palmitoleic acid (μg/mL)	Perilla oil	64.77 ± 25.50	73.94 ± 39.24	0.247
	Olive oil	65.75 ± 37.47	73.91 ± 33.71	0.445
Stearic acid (μg/mL)	Perilla oil	260.59 ± 41.50	274.05 ± 45.73	0.106
	Olive oil	262.54 ± 43.77	276.61 ± 57.94	0.346
Oleic acid (μg/mL)	Perilla oil	740.99 ± 233.84	776.63 ± 258.10	0.503
	Olive oil	718.07 ± 198.32	831.36 ± 306.45	0.219
Linoleic acid (μg/mL)	Perilla oil	1166.83 ± 146.40	1155.99 ± 115.14	0.654
	Olive oil	1154.53±119.03	1169.50 ± 216.89	0.799
γ-linolenic acid (μg/mL)	Perilla oil	13.84 ± 5.74	12.25 ± 3.03	0.394
	Olive oil	14.07 ± 3.57	14.31 ± 3.87	0.891
Arachidic acid (μg/mL)	Perilla oil	9.37 ± 1.53	9.59 ± 1.57	0.340
	Olive oil	9.38±1.54	9.55 ± 1.57	0.623
Eicosenoic acid (μg/mL)	Perilla oil	5.35 ± 2.05	5.17±1.88	0.515
	Olive oil	4.76 ± 1.32	5.78 ± 3.33	0.276
Eicosadienoic acid (μg/mL)	Perilla oil	8.89 ± 2.30	8.63 ± 2.43	0.562
	Olive oil	8.48 ± 1.85	8.94±3.35	0.604
5–8–11 eicosatrienoic acid (μg/mL)	Perilla oil	3.18±0.82	2.9 ± 1.31	0.410
	Olive oil	2.96 ± 1.04	3.26 ± 1.18	0.387
Dihomo-γ-linolenic acid (μg/mL)	Perilla oil	47.76 ± 9.52	44.83 ± 13.35	0.242
	Olive oil	51.63 ± 21.62	51.38 ± 16.84	0.945
Arachidonic acid (μg/mL)	Perilla oil	261.62 ± 42.74	253.67 ± 50.44	0.261
	Olive oil	267.28 ± 45.99	258.96 ± 44.81	0.226
Behenic acid (μg/mL)	Perilla oil	25.2 ± 5.21	25.59 ± 5.14	0.607
	Olive oil	25.83 ± 4.67	25.64 ± 5.00	0.785
Erucic acid (μg/mL)	Perilla oil	1.04 ± 0.07	1.12±0.14	0.121
	Olive oil	1.09 ± 0.12	1.14 ± 0.21	0.475
Docosatetraenoic acid (μg/mL)	Perilla oil	6.82 ± 1.36	6.67 ± 1.80	0.726
	Olive oil	6.77 ± 1.53	7.04 ± 2.02	0.666
Docosapentaenoic acid (μg/mL)	Perilla oil	19.82 ± 5.39	22.67 ± 8.14	0.126
	Olive oil	20.24 ± 5.70	19.5 ± 6.72	0.505
Lignoceric acid (μg/mL)	Perilla oil	22.14 ± 3.74	22.57 ± 4.06	0.580
	Olive oil	22.68 ± 2.91	22.52 ± 3.93	0.778
Docosahexaenoic acid (μg/mL)	Perilla oil	139.94 ± 42.19	142.82 ± 48.54	0.644
	Olive oil	152 ± 51.35	140.64 ± 42.32	0.134
Nervonic acid (μg/mL)	Perilla oil	42.39 ± 7.28	41.71 ± 5.64	0.641
	Olive oil	43.76 ± 6.12	42.04 ± 5.86	0.197

Values are presented as mean ± standard deviation; n = 10.

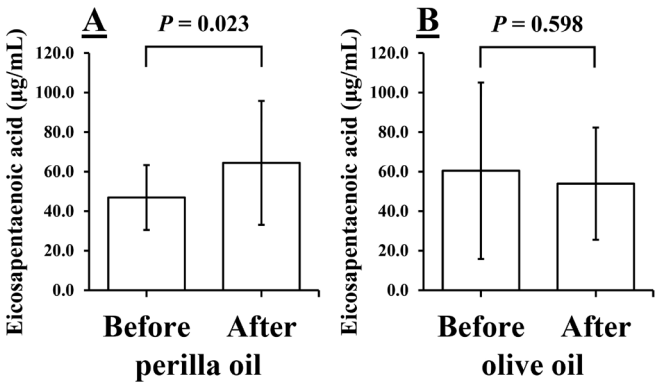

Figure 3. Levels of Eicosapentaenoic acid before and after 1 week of intake of perilla oil (A) or olive oil (B). Values are presented as mean ± standard deviation; n = 10.

Safety. There were no serious adverse events related to the intervention. There were also no significant changes in WBC, RBC, and platelet counts after ingestion of perilla oil.

Discussion

Prevention of arteriosclerosis which leads to cardiovascular disease is very important [17]. Given its apparent preventing effects, we focused our experiments on ALA and confirmed that a week's daily intake of perilla oil significantly increased the plasma levels of ALA and EPA. It has been reported that 11% to 19% of ALA ingested from a meal is converted to EPA or DHA through an in vivo chain extension process [18]. In this study, ALA and EPA increased significantly after intake of perilla oil.. The levels of LDL-C and HDL-C were not changed after intake of perilla oil, while the LDL-C/HDL-C ratio was significantly improve. Recently, the LDL-C/HDL-C ratio has been regarded as an important index of arteriosclerosis. Even in the presence of normal levels of LDL-C, myocardial infarction may occur with low levels of HDL-C. Prevention of arteriosclerosis thus necessitates balancing the levels of LDL-C and HDL-C, which supports the concept of the LDL-C/HDL-C ratio as an important index [19, 20]. Previous study has been reported that Omega - 3 polyunsaturated fatty acids treatments reduced serum total cholesterol and LDL-C and increased HDL-C [21]. Improving of HDL-C / LDL-C ratio is important for prevention of arteriosclerosis [22]. Improving the ratio would be important to reduce arteriosclerosis risk.

No other significant differences except the changes in the LDL-C/HDL-C ratio and levels of ALA and EPA after ingestion of perilla oils were found in any of the variables we measured. There were no changes in blood pressure or BMI. Overdoses of ALA, EPA, and DHA may affect blood coagulation [15]. However, the platelet counts in our subjects did not change significantly before and after ingestion of perilla oil, and no adverse events related to blood clotting were occurred. No adverse events occurred. Therefore, the daily ingestion of perilla oil for 1 week appears to be safe.

RHI evaluates the vasodilator functions of vascular endothelium-derived vasodilators [23]. In this study, RHI was measured as an indicator of vascular endothelial function. Long-term treatment with EPA has been reported to improve impaired endothelium-dependent relaxations of atherosclerotic blood vessels [24]. In this study, we expected that the RHI might improve by perilla oil-induced increases in ALA, but there was no significant difference in the RHI before and after perilla oil.

Because ours was a short-term study with ingestion of perilla oil occurring for only 1 week and involving a small number of subjects, the study may have been underpowered to detect a significant difference in the RHI. Future studies in large numbers of individuals with long-term intake of perilla oil are needed.

Conclusion

We confirmed significant increases in the plasma levels of ALA and improvement in the LDL-C/HDL-C ratio induced by intake of perilla oil. To the extent that improvement of those markers may have a preventive effect against arteriosclerosis, our study suggests that ingestion of perilla oil may be of value in decreasing or preventing arteriosclerosis. Confirming this hypothesis will require long-term administration of perilla oil supplementation and adequate numbers of subjects so that cardiovascular outcomes can be assessed.

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Conflict of Interest

No potential conflicts of interest were disclosed.

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