

Multiple functions of policosanol in elderly patients with dyslipidemia

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Abstract

Objective: To determine the multiple functions of policosanol in elderly dyslipidemia patients.

Methodology: There were 294 elderly dyslipidemia patients enrolled into this clinical study. They were randomly divided into four groups, as follows: 20 mg policosanol (group A, n = 64); 10 mg policosanol (group B, n = 72); 20 mg atorvastatin (group C, n = 91); and 10 mg policosanol + 20 mg atorvastatin (group D, n = 62). Plasma platelet count, platelet aggregation rate, circulating endothelial cell (CEC) count, high sensitivity C-reactive protein (hs-CRP), and carotid intima-media thickness (IMT) were measured before the study (week 0) and at weeks 12, 24, and 52.

Results: In group A, the platelet aggregation rate caused by adenosine diphosphate (ADP) after treatment was significantly decreased compared with before treatment ($48.79\% \pm 20.29\%$ vs. $40.37\% \pm 23.56\%$), but the arachidonic acid (AA)-induced platelet aggregation rates were similar. The platelet aggregation rates induced by AA and ADP in groups B, C, and D did not change significantly. CEC counts and hs-CRP and homocysteine levels in all groups after treatment were significantly lower compared with before treatment, but carotid IMTs were similar.

Conclusion: Policosanol regulates blood lipid levels and improves endothelial cell function, and it could delay the progress of atherosclerosis.

Trial registration number: ChiCTR-RRC-17013396 (retrospectively registered).

Keywords

Policosanol, atorvastatin, elderly, dyslipidemia, endothelial cell, atherosclerosis

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Introduction

Policosanol is a new lipid-regulating drug that was extracted from sugar cane wax, and the lipid-lowering effect of policosanol and its safety have been confirmed. Polyalcohols contain a mixture of eight major fatty alcohols,¹ and the proportion of each fatty alcohol is fairly stable, with octacosanol having the highest molecular weight (410.5 kDa).² In the process of acetate consumption and mevalonate synthesis, docosanol inhibited cholesterol biosynthesis, but it did not directly inhibit 3-hydroxy-3-methylglutaryl-coenzyme A (HMG CoA) activity. Docosanol can also increase low-density lipoprotein (LDL) uptake by liver cells by increasing the number of LDL receptors, which reduces LDL-cholesterol (C) levels and serum LDL transport. Foreign data showed that docosanol 10 mg/day can reduce LDL-C by 27.8%, reduce total cholesterol (TC) by 21.8%, increase high-density lipoprotein cholesterol (HDL-C) by 11.3%, and reduce the TC-to-HDL-C ratio by 25 to 40%.³ In addition to lowering serum LDL-C levels, animal experiments have also shown that polyalcohol can reduce cholesterol levels in the aorta, heart, liver, and adipose tissue. Animal experiments also confirmed that polyalcohol can inhibit lipid peroxidation, inhibit platelet aggregation that is mediated by collagen and adenosine diphosphate (ADP), reduce thromboxane (TXB) levels, increase prostacyclin (PGI) levels, and inhibit endothelial smooth muscle cell proliferation. These effects suggest that policosanol may prevent atherosclerosis.^{4,5}

In the elderly population, the use of policosanol in people aged 60 to 85 years old has a similar or greater effect compared with its use in young people.^{6,7} However, few studies have been performed in the elderly population. Policosanol also has multiple functions besides regulating blood

lipid levels, such as increasing the platelet aggregation rate and inhibiting endothelial thickening and smooth muscle proliferation, thereby decreasing atherosclerosis.^{5,8} In this study, we preliminarily explored the role of policosanol in the regulation of blood lipids in elderly patients with cardiovascular diseases.

Methods and materials

Ethics approval

The clinical trial registration number is ChiCTR-RRC-17013396 (retrospectively registered).

The study was approved by the Institutional Ethics Committee of South Building, Chinese PLA General Hospital, and written informed consent was obtained from all participants.

Subjects

There were 294 elderly patients with dyslipidemia who were treated at our hospital from September 2010 to September 2012, and who were enrolled into our clinical trial.

The inclusion criteria were as follows: (1) age ≥ 75 years; (2) results of intravenous blood sampling before enrollment were TC ≥ 5.72 mmol/L or/and LDL-C ≥ 2.07 mmol/L with or without hypertriglyceridemia; and (3) not taking lipid-regulating drugs except policosanol tablets and atorvastatin calcium tablets.

The exclusion criteria were as follows: (1) Allergy to any component of polydose and/or atorvastatin calcium tablets; (2) patients with cerebrovascular accident, severe trauma, or major surgery, or digestive system ulcer bleeding within 6 months before enrollment; (3) patients with nephrotic syndrome, thyroid dysfunction, or acute and chronic liver and gallbladder diseases; (4) hyperlipidemia caused by drugs

(e.g. phenothiazines, beta-blockers, and adrenal corticosteroids); (5) patients with severe blood and clotting disorders; (6) patients with severe alcohol abuse; or (7) patients who had received other drug tests within 6 months before the study.

Grouping

All patients enrolled into this clinical study were randomly divided into four groups, as follows: group A ($n=64$) patients took 20 mg of policosanol (two tablets) daily before bedtime; group B ($n=72$) patients took 10 mg of policosanol (one tablet) daily before bedtime; group C ($n=91$) patients took 20 mg of atorvastatin calcium (one tablet) daily before bedtime; or group D ($n=62$) patients took 10 mg of policosanol (one tablet) and 20 mg of atorvastatin calcium (one tablet) daily before bedtime.

Observation indices

All selected patients were randomly divided into groups based on the test plan, while receiving lifestyle adjustment therapy such as diet control, weight monitoring, and physical exercise. The patients' general demographic information was recorded, including their name, gender, height, and weight. The patients' medical history was recorded, including coronary heart disease (CHD), diabetes mellitus (DM), hypertension (HP), and chronic obstructive pulmonary disease (COPD) as well as their history of smoking and family history of cardiovascular diseases. The patients received the corresponding test drug treatment based on the randomized groupings, with an observation period of 52 weeks. The patients were regularly asked about adverse events and conditions after drug administration, including abdominal discomfort, muscle pain, fatigue, allergies, gastrointestinal discomfort, and other adverse reactions. During the clinical trial, the patients were

instructed to avoid taking lipid-regulating drugs except for the test drugs, such as other statins, fibrates, nicotinic acids, cholic acid chelating agents, and cholesterol absorption inhibitors.

Fasting venous blood was drawn routinely in the morning before the study (week 0) and at weeks 12, 24, and 52 during the study. Blood indicators, as described below, were monitored by a skilled professional technician in the clinical laboratory at our hospital.

The platelet aggregation rate, platelet (PLT) count, high sensitivity C-reactive protein (hs-CRP), and homocysteine (Hcy) were measured using arachidonic acid (AA) at a concentration of 0.5 mg/L and adenosine diphosphate (ADP) at a concentration of 10 $\mu\text{mol/L}$ as inducers.

The circulating endothelial cell (CEC) count was determined. Briefly, 2 mL of blood was drawn into ethylenediamine tetraacetic acid (EDTA) tubes in the morning after the patient had fasted overnight, and the cells were harvested into the flow tube. Then, 3 μL of CD146 and 1 μL of CD146-APC were added into each tube, and the cells were stained in the dark for 15 minutes. PBS (1 mL) was added and the sample was centrifuged at $150 \times g$ for 5 minutes to remove the supernatant, and 300 μL of rupture agent was added. The samples were incubated in the dark for 20 minutes, and 1.5 mL of rupture fluid was added. The samples were centrifuged at $170 \times g$ for 5 minutes and the supernatant was discarded. An additional 1 mL of rupture fluid was then added and centrifuged at $170 \times g$ for 5 minutes and the supernatant was discarded. The sample was then fixed using 400 μL of paraformaldehyde. Samples were analyzed within 24 hours. Cellquest software (BD Biosciences, San Jose, CA, USA) was used for testing and FlowJo software (Becton Dickinson and Co., Franklin Lakes, NJ, USA) was used for the analysis. The results were expressed as cell/ μL .

The reagent was HU CD146 PE MAB (BD Pharmingen, San Diego, CA, USA).

Carotid ultrasonography was also performed. Intra-media thickness (IMT) monitoring was performed before and after study drug administration, and the procedure was performed by an ultrasound specialist.

Statistical analysis

Power Analysis and Sample Size (PASS) software (Keyville, UT, USA) was used to estimate sample size. All data were analyzed using SPSS version 13.0 (SPSS Inc., Chicago, IL, USA). The categorical data that showed a normal distribution were expressed as mean \pm standard deviation (SD). Count data were expressed using the frequency and relative number (composition ratio and rate). Inter-group comparisons were conducted by a *t*-test, and multi-group comparisons were performed using by the F test. An independent *t*-test or F-test was used to compare the normal measurement data with the measurement data that were normally distributed, and the Kolmogorov–Smirnov nonparametric test was used to analyze the measurement data that were not normally distributed. The numerical data were expressed as case number and percentage, and subjected to the Chi-square test. The Chi-square test was used to analyze and compare the differences between groups by single factor analysis. Before statistically analyzing the data, a homogeneity test of variance was

performed. Double sided tests were used, and $P < 0.05$ was considered to be statistically significant.

Results

Baseline clinical data

Demographic information. Patients' demographic information is presented in Table 1. There were 294 elderly patients with dyslipidemia who were treated at our hospital from September 2010 to September 2012 and who were enrolled into our clinical trial. There were no differences in the demographic information between the study groups at baseline (week 0). Among these patients, there were two patients who died of a malignant tumor and three patients who were lost to follow-up. At the end of the 1-year follow-up period (week 52), there were 289 patients remaining, and their average age was 84.62 ± 5.66 years (range, 75–98 years). Among these patients, 258 were men and 31 were women. The patients' systolic and diastolic blood pressure ranged from 130 to 160/80 to 110 mmHg. Additionally, all patients met the study entry criteria as follows: TC was ≥ 5.72 mmol/L and LDL-C was ≥ 2.07 mmol/L with or without hypertriglyceridemia (i.e. TG ≥ 2.3 mmol/L).

Chronic disease comorbidities, smoking history, and family history of cardiovascular diseases. Before the study, all groups had similar chronic disease comorbidities, such as

Table 1. Demographic information.

	Group A	Group B	Group C	Group D
n (case)	64	72	91	62
Age (years)	85.41 \pm 4.33	86.34 \pm 4.83	84.39 \pm 4.01	85.45 \pm 5.29
Male (%)	58 (90.62)	62 (87.5)	83 (91.21)	54 (87.1)
Female (%)	6 (9.38)	9 (12.5)	8 (8.79)	8 (12.9)
BMI (kg/m ²)	21.94 \pm 2.31	22.62 \pm 2.82	22.41 \pm 2.09	23.07 \pm 2.64

BMI, body mass index.

CHD, DM, HP, and COPD. Additionally, the groups all had a similar family history of cardiovascular disease and smoking history (Table 2).

Antiplatelet drugs. Before the study, all groups had taken similar types and doses of antiplatelet drugs (Table 3).

Platelet levels before and after treatment. All groups had similar PLT levels before and after treatment (Table 4).

Platelet aggregation rates before and after treatment. Before treatment, the PLT aggregation rates that were induced by AA and ADP in all groups were similar. In group A,

Table 2. Comorbid chronic diseases, smoking history, and family history.

	Group A	Group B	Group C	Group D
n (case)	64	72	91	62
CHD (%)	57 (89.06)	65 (90.28)	83 (91.21)	57 (91.94)
HP (%)	53 (82.81)	60 (83.33)	79 (86.81)	49 (79.03)
DM (%)	37 (57.81)	39 (54.17)	51 (56.04)	35 (56.45)
COPD (%)	29 (45.31)	31 (43.06)	38 (41.76)	27 (43.55)
Smoking history (%)	31 (48.43)	37 (51.38)	43 (47.25)	29 (46.77)
Family history (%)	42 (65.62)	44 (61.11)	52 (57.14)	38 (61.29)

CHD, coronary heart disease; HP, hypertension; DM, diabetes mellitus; COPD, chronic obstructive pulmonary disease.

Table 3. Use of antiplatelet drugs.

	Group A	Group B	Group C	Group D
n (case)	64	72	91	62
Single use of aspirin (%)	25 (39.07)	29 (40.28)	36 (39.56)	24 (38.71)
Single use of clopidogrel (%)	15 (23.45)	16 (22.22)	20 (21.98)	13 (20.97)
Combined use of two antiplatelet drugs (%)	17 (26.56)	20 (27.78)	24 (26.37)	19 (30.65)
Use of other antiplatelet drugs (%)	3 (4.69)	3 (4.17)	5 (5.49)	3 (4.84)
Not taking antiplatelet drugs (%)	4 (6.25)	4 (5.56)	6 (6.59)	4 (6.45)

Table 4. PLT levels before and after treatment.

Week	Group A (n = 64)	Group B (n = 72)	Group C (n = 91)	Group D (n = 62)
PLT ($\times 10^9/L$)				
0	175.31 \pm 86.80	177.46 \pm 92.34	189.76 \pm 83.28	179.51 \pm 79.77
52	179.79 \pm 78.46	173.96 \pm 89.32	183.63 \pm 79.99	194.78 \pm 86.92
Platelet aggregation rate (AA, %)				
0	38.82 \pm 29.41	39.16 \pm 28.79	42.57 \pm 31.28	41.99 \pm 30.47
52	40.69 \pm 28.71	38.62 \pm 31.59	41.93 \pm 33.77	40.87 \pm 28.99
Platelet aggregation rate (ADP, %)				
0	48.79 \pm 20.29	46.42 \pm 21.87	47.76 \pm 21.49	46.77 \pm 19.75
52	40.37 \pm 23.56 [#]	47.99 \pm 22.65	45.21 \pm 22.89	48.21 \pm 20.71

[#]Compared with week 0, $P < 0.05$.

PLT, platelet; AA, arachidonic acid; ADP, adenosine diphosphate.

the platelet aggregation rate that was induced by ADP after treatment was significantly lower compared with before treatment ($P < 0.05$), but the AA-induced platelet aggregation rates were similar before and after treatment. The platelet aggregation rates that were induced by AA and ADP in group B, group C, and group D did not change significantly (Table 5).

CEC counts before and after treatment. Before treatment, CEC counts in all groups were similar. CEC counts in all groups after treatment were significantly lower compared with before treatment ($P < 0.05$; Table 5).

IMT, hs-CRP, and Hcy levels before and after treatment. Before treatment, all groups had similar IMT, hs-CRP, and Hcy levels. hs-CRP and Hcy levels in all groups after

treatment were significantly lower compared with before treatment ($P < 0.05$), but carotid IMTs were similar (Table 6).

Discussion

Blood lipid management has always been the top priority in the prevention and treatment of CHD. In 2014, experts on the prevention and treatment of blood lipid abnormalities proposed that LDL-C in extremely high-risk groups, such as in unstable angina pectoris patients, should be controlled at a strict level of ≤ 1.8 mmol/L.⁹ When using conventional statin doses, some patients cannot achieve the above goals,¹⁰ and the risk of cardiovascular events is not fully controlled. Therefore, a combination of drugs may be a more suitable lipid regulation strategy for the elderly. Numerous studies at home and abroad have shown that many nutritious

Table 5. CEC counts before and after treatment.

Week	Group A (n = 10)	Group B (n = 10)	Group C (n = 10)	Group D (n = 10)
CEC (cell/ μ L)				
0	4.01 \pm 1.92	4.11 \pm 1.88	4.09 \pm 1.94	4.00 \pm 1.92
52	3.57 \pm 1.89 [#]	3.61 \pm 1.91 [#]	3.50 \pm 1.91 [#]	3.45 \pm 1.97 [#]

[#]Compared with week 0, $P < 0.05$.
CEC, circulating endothelial cell.

Table 6. IMT, hs-CRP and Hcy levels before and after treatment.

Week	Group A (n = 64)	Group B (n = 72)	Group C (n = 91)	Group D (n = 62)
IMT (mm)				
0	13.22 \pm 6.13	13.11 \pm 6.01	13.21 \pm 5.89	13.09 \pm 6.08
52	12.98 \pm 5.99	13.05 \pm 6.19	12.92 \pm 6.04	13.00 \pm 5.89
hs-CRP (mg/dL)				
0	3.82 \pm 2.46	3.89 \pm 2.72	4.01 \pm 2.89	3.72 \pm 2.76
52	2.78 \pm 1.99 [#]	2.98 \pm 1.98 [#]	2.76 \pm 1.77 [#]	2.62 \pm 1.69 [#]
Hcy (μ mol/L)				
0	29.12 \pm 9.38	30.72 \pm 10.26	32.69 \pm 11.73	31.77 \pm 10.98
52	27.89 \pm 9.68 [#]	28.73 \pm 9.78 [#]	28.34 \pm 9.99 [#]	28.57 \pm 10.77 [#]

[#]Compared with week 0, $P < 0.05$.

IMT, intima-media thickness; hs-CRP, high sensitivity C-reactive protein; Hcy, homocysteine.

foods or plant extracts can regulate blood lipids and reduce the risk of heart and metabolic diseases.^{11–14}

Policosanol is a novel regulator of lipid-lowering drugs. It is a mixture of eight long-chain aliphatic primary alcohols that are specially treated with organic solvents, and it was discovered by Cuban scientists during the extraction of sugarcane wax.¹⁵ It has been confirmed that policosanol can significantly reduce LDL-C and TC levels, increase HDL-C levels, reduce LDL lipid peroxidation sensitivity, and delay the progression of atherosclerosis.¹⁶ In addition to a clear lipid-lowering effect, policosanol has a pleiotropic effect, such as anti-oxidation, inhibition of platelet aggregation rate, inhibition of smooth muscle cell proliferation and intimal hyperplasia, stabilization of the atherosclerotic plaque, improvement of vascular endothelial function, and prevention of atherosclerosis development. Polypinol has a slightly lower effect on lowering LDL-C levels compared with atorvastatin at the same dose or pravastatin at the same dose, which is within the conventional dose range (10–40 mg/day). It has medium-intensity lipid-lowering effects based on China¹⁷ and European and American¹⁸ guidelines for blood lipid prevention and control. In this study, the pleiotropic effect of policosanol on cardiovascular diseases in elderly patients was preliminarily studied and compared with that of atorvastatin calcium tablets.

Studies have reported that daily administration of policosanol at a dose greater than 10 mg can significantly reduce TXB levels and inhibit ADP-induced platelet aggregation.¹⁹ In this study, the platelet aggregation rate that was induced by ADP in the 20 mg policosanol group was decreased, but the platelet aggregation rate that was induced by AA was not significantly changed. In addition, no significant change was found in the platelet aggregation rate (AA, ADP induction)

after long-term use of 10 mg of policosanol, 20 mg of atorvastatin, or 20 mg atorvastatin + 10 mg policosanol. In this study, most of the enrolled patients had been taking oral anti-platelet drugs, and their dose and type varied to some extent. No antiplatelet drugs were discontinued and the dose or type of anti-platelet drugs was not adjusted during the study. This affected the experimental results, and the role of policosanol in improving platelet aggregation function requires further confirmation.

Vascular endothelial cell injury is an initiator of atherosclerotic lesions. Under normal conditions, less than 1% of endothelial cells are replaced daily, so the number of CECs in the body is very small. However, in the pathological state of endothelial injury, the number and morphology of CECs will change.²⁰ Takahashi et al.²¹ proposed that the circulatory endothelial cell count is an *in vivo* marker that can directly reflect vascular endothelial injury through an increase in the number of CECs. This study showed that 20 mg of atorvastatin calcium could effectively reduce the number of CECs, improve endothelial function, and maintain endothelial cell stability. Similarly, both 10 mg and 20 mg of policosanol could reduce the CEC count and improve endothelial function. However, the combined application of 10 mg policosanol + 20 mg atorvastatin did not show a cumulative effect.

The relationship between Hcy and hs-CRP and atherosclerosis has been extensively studied in recent years. Studies have suggested that Hcy levels can be used as a non-invasive indicator of coronary vascular lesions.²² hs-CRP has been shown to be an independent risk factor for cardiovascular diseases that are caused by chronic inflammation. Monitoring the hs-CRP concentrations can help to determine the likelihood of cardiovascular diseases and their acute events.²³ In this study, compared with before treatment, Hcy and hs-CRP levels

were significantly lower after treatment with 20 mg or 10 mg policosanol, 20 mg atorvastatin, and 20 mg atorvastatin + 10 mg policosanol. There was no statistically significant difference in the decrease in Hcy and hs-CRP levels compared with the 20 mg policosanol and 20 mg atorvastatin groups. Animal experiments have confirmed that policosanol can inhibit P38MAPK phosphorylation to a certain extent, and reduce the expression of atherosclerotic genes, blood lipids, hs-CRP levels and other serum inflammatory factors, and endothelial injury to promote an anti-inflammatory effect in atherosclerosis.²⁴ In this study, before and after treatment, no carotid atherosclerotic plaque progress was found in the 20 mg policosanol group or the 10 mg policosanol group, and the same as the results were found in the 20 mg atorvastatin group.

Limitations

This study has some potential limitations. Because of the relatively small number of subjects and samples in this study, the test results may be affected to a certain extent. Thus, the role of policosanol in the inhibition of platelet aggregation needs to be further studied by choosing patients who are not taking antiplatelet drugs.

Conclusion

In addition to regulating blood lipid levels, policosanol also can improve endothelial function and mitigate atherosclerosis.

Declaration of conflicting interest


The authors declare that there is no conflict of interest.

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References

1. Castaño G, Tula L, Canetti M, et al. Effects of policosanol in hypertensive patients with type II hypercholesterolemia. *Current Therap Res* 1996; 57: 691–699. DOI: [https://doi.org/10.1016/S0011-393X\(96\)80074-9](https://doi.org/10.1016/S0011-393X(96)80074-9).
2. Menéndez R, Marrero D, Más R, et al. In vitro and in vivo study of octacosanol metabolism. *Arch Med Res* 2005; 36: 113–119.
3. Castaño G, Más R, Fernández JC, et al. Effects of policosanol on older patients with hypertension and type II hypercholesterolaemia. *Drugs R D* 2002; 3: 159–172.
4. Castaño G, Más R, Arruzazabala ML, et al. Effects of policosanol and pravastatin on lipid profile, platelet aggregation and endothelium in older hypercholesterolemic patients. *Int J Clin Pharmacol Res* 1999; 19: 105–116.
5. Menéndez R, Amor AM, Rodeiro I, et al. Policosanol modulates HMG-CoA reductase activity in cultured fibroblasts. *Arch Med Res* 2001; 32: 8–12.
6. Kim JY, Kim SM, Kim SJ, et al. Consumption of policosanol enhances HDL functionality via CETP inhibition and reduces blood pressure and visceral fat in young and middle-aged subjects. *Int J Mol Med* 2017; 39: 889–899.
7. Fernández S, Más R, Gamez R, et al. A pharmacological surveillance study of the tolerability of policosanol in the elderly population. *Am J Geriatr Pharmacother* 2004; 2: 219–229.
8. Francini-Pesenti F, Spinella P and Calò LA. Potential role of phytochemicals in metabolic syndrome prevention and therapy. *Diabetes Metab Syndr Obes* 2019; 12: 1987–2002.

9. Jellinger PS. American Association of Clinical Endocrinologists/American College of Endocrinology management of dyslipidemia and prevention of cardiovascular disease clinical practice guidelines. *Diabetes Spectr* 2018; 31: 234–245.
10. Ping Y and Xiaoying L. Chinese Geriatric Society, writing group of Chinese Expert Consensus on the treatment of sensile dyslipidemia with policosanol. Chinese expert consensus on the treatment of sensile dyslipidemia with policosanol. *Chin J Geriatri* 2017; 36: 831–835.
11. Patti AM, Al-Rasadi K, Giglio RV, et al. Natural approaches in metabolic syndrome management. *Arch Med Sci* 2018; 14: 422–441.
12. Cicero AFG, Colletti A, Bajraktari G, et al. Lipid-lowering nutraceuticals in clinical practice: position paper from an International Lipid Expert Panel. *Nutr Rev* 2017; 75: 731–767.
13. Sahebkar A, Serban MC, Gluba-Brzózka A, et al. Lipid-modifying effects of nutraceuticals: an evidence-based approach. *Nutrition* 2016; 32: 1179–1192.
14. Cicero AFG, Fogacci F and Colletti A. Food and plant bioactives for reducing cardiometabolic disease risk: an evidence based approach. *Food Funct* 2017; 8: 2076–2088.
15. Mas R, Castaño G, Fernández J, et al. Long-term effects of policosanol on obese patients with type hypercholesterolemia. *Asia Pac J Clin Nutr* 2004; 13: S102–S108.
16. Janikula M. Policosanol: a new treatment for cardiovascular disease? *Altern Med Rev* 2002; 7: 203–217.
17. Yuan-Lin G, Li J-J. Highlights of the guidelines for prevention and treatment of dyslipidemia in Chinese adults (Revised Edition 2016). *Chinese Journal of the Frontiers of Medical Science (Electronic Version)*. 2017; 31: 937–953.
18. Catapano AL, Graham I, De Backer G, et al. 2016 ESC/EAS guidelines for the management of dyslipidaemias: the task force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS) developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). *Atherosclerosis* 2016; 253: 281–344.
19. Singh U, Dasu MR, Yancey PG, et al. Human C-reactive protein promotes oxidized low density lipoprotein uptake and matrix metal-loproteinase-9 release in Wistar rats. *J Lipid Res* 2008; 49: 1015–1023.
20. Han JQ, Li BW, Yuan XC, et al. Circulating endothelial cells: important biomarkers for evaluating vascular endothelial functions in the pathological state. *J Chin Microcirc* 2009; 13: 431–435.
21. Takahashi H and Harker LA. Measurement of human endothelial cells in whole blood. *Thromb Res* 1983; 31: 22–23.
22. Kazemi MB, Eshraghian K, Omrani GR, et al. Homocysteine level and coronary artery disease. *Angiology* 2006; 57: 9–14.
23. Arenillas JF, Alvarez-Sabin J, Molina CA, et al. C-reactive protein predicts further ischemic events in first-ever transient ischemic attack or stroke patients with intracranial large-artery occlusive disease. *Stroke* 2003; 34: 2463–2468.
24. Li JJ, Tian NL, Zhu ZS, et al. Characterization of the molecular mechanism of anti-atherosclerotic effect of policosanol in atherosclerosis rats. *Acta Univ Med Nanjing (Nat Sci)* 2012; 23: 650–654.