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Original Article

Anti-atherosclerosis action of the traditional Korean medicine Bok Ryung Ban Ha -Tang in ApoE KO mice

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Abstract: Atherosclerosis is characterized by vascular obstruction from the deposits of plaque, resulting in reduced bloo flow. Here, we investigate that dynamic changes of bodyweight, liver weight, lipid levels, atherosclerotic lesion and liver steatosis, during the progression of atherosclerosis in ApoE KO mice. Male ApoE KO mice were fed a high fat diet (western type diet, WD) for 16 weeks. BRBHT; Bok Ryung Ban Ha -Tang, treatment of WD-fed atherosclerosis mice significantly reduced body weight, liver weight, blood pressure and lipid levels relative to the WD-fed mice. Lipid levels of T-chole, LDL, TG, Glucose were significantly decreased in the BRBHT treat mice compared with the WD-fed mice, also AST, ALT were significantly chaged in the BRBHT mice compared with the levels in the WD mice. Histological examination showed that the atherosclerotic lesions were reduced in the WD with BRBHT group compared with the WD group. Furthermore, the administration of BRBHT decreased fat accumulation in hepatic. Taken together, the present data indicate that BRBHT prevents atherosclerosis in WD-induced ApoE KO mice by regulation of lipid and liver steatosis.

Keywords: Atherosclerosis, apolipoprotein E-deficient mice, Bok Ryung Ban Ha -Tang, liver steatosis, cholesterol

Introduction

Atherosclerosis is multifactorial disease of the large arteries and the leading cause of morbidity and mortality in industrialized countries [1, 2]. Early atherosclerotic lesions are characterized by the accumulation of fatty streaks consisting of abnormal lipids, lipid-laden foam cells in the vessel wall intima. With disease progression, more complicated inflammatory processes are involved and atherosclerotic plaques are covered with fibrous caps form in the aortic vessel walls [3]. Furthermore, High blood pressure is a major cause of atherosclerosis, the artery-clogging process that leads to heart attacks and strokes [4].

Numerous pharmacological approaches for the prevention and treatment of atherosclerosis have been suggested. Treatmetn for atherosclerosis may include lifestyle changes, medical surgery and the administration of drugs that prevent blood clots by lower cholesterol or blood pressure [5]. Clinically available anti-atherosclerosis agents include Statin (HMG-CoA reducatase inhibitors), which is a centrally acting in the production of cholesterol in the liver [6]. However, these agents have been reported to cause undersirable side-effects, including pain, tiredness, liver and muscle problems with ocular (such as, blurred vision) side effects [7]. Therefore, due to the limited usage of these pharmacological agents, there is a demand for alternative therapies, including the use of herbal products, that have minimal side effects [8]. For example, Doinseungi-tang, a traditional herbal medicine composed of 5 species, has been reported to be an effective treatment for atherosclerosis. In particular, Doinseungo-tang reduced atherosclerotic lesion and lipid levels [9].

Bok Ryung Ban Ha -Tang, which is one of the herbal mixtures. In prescription is three species composed of *Pinellia ternata* (Thunb.) Breit, *Wolfiporia extensa*, *Zingiber officinale*, that have various pharmacological on the traditional medicinal prescription has been used orally for

Table 1. Composition of Bok Ryung Ban Ha -Tang

Scientific name	Herbal name	Amount (g)
Pinellia ternata (Thunb.) Breit	Pinellia Tuber	120
Wolfiporia extensa	Poria cocos	80
Zingiber officinale	Ginger	80

promoting blood circulation to remove blood stasis and anti-inflammation [10].

Traditional Korean herbal medicine has been widely used in the treatment of atherosclerosis-related disorders [11]. However, the anti-atherosclerosis effects of BRBHT have not previously been studied. In this study, we investigated the effects of BRBHT on bodyweight, serum lipid levels, atherosclerotic lesion and liver steatosis WD-induced atherosclerosis

Materials and methods

Preparation of BRBHT

The herbs were purchased from Naemome-Dah Medicinal Herbs Co. (Ulsan, Korea) and authenticated based on their microscopic and macroscopic characteristics by the classification and identification committee of the Korea Institute of Oriental Medicine (KIOM).

The formula of BRBHT consists of three herbs, including *Pinellia ternata (Thunb.)* (120 g), *Poria cocos* (80 g), *Zingiber officinale Rosc.* (80 g), which were mixed and ground into a crude powder. The total mixure (280 g) was boiled in distilled water (1:10, v/v) at 100°C for 2 h and the extract was filtered, lyophilized and subsequently stored at -20°C. The yield of BRBHT aqueous extract was 11.25% (w/w) (**Table 1**).

Experimental animals

Male *ApoE* Knockout mice (*ApoE* KO, Japan SLC Inc., Shizuoka, Japan) mice having a of C57BL/6J genetic background were housed under diurnal lighting conditions and alloed food and tap water ad libitum. All of the animal procedures were in accordance with the institutional guidelines for animal research and were approved by the Korea Institute of Oriental Medicine (KIOM). To induced atherosclerosis, Eight-weeks-old *ApoE* KO Mice were fed a western type High Fat Diet (41% of total calories from fat; 0.21% cholesterol; Research Diet, New Brunswick, NJ, USA) for 16 weeks. The control mice were fed a commercial standard chow diet (Orient Bio Inc., Seongnam, Korea) consisting of 14% energy as fat, 21% as protein and 65% as carbohydrates. Atorvastatin were used as positive controls. The mice ere randomly divided into four groups (n=8) and fed a normal diet (control), a WD, a WD+BRBHT, a WD+Atorvastatin for 16 weeks. BRBHT was administered to the mice at a dose of 150 mg/kg/day and Atrorvastatin administerd 10 mg/kg/day. By contrast, the normal saline was orally administerd to the mice in the control-fed and WD-fed control group.

Body weight and blood pressure

Body weight were measured once a week and Blood pressure was monitored using a noninvasive tail-cuff CODA™ system (Kent Scientific; Torrington, CT, USA) as previously described [12].

Liver weight

Subsequent to blood collection, the livers were removed from the mice and immediately weighted.

Analysis of serum markers

Blood was collected from the aorta under light anesthesia and stored on ice for 30 min before centrifugation at 13,000 rpm at 4°C for 10 min, after which they were stored at -80°C. Serum levels of T-chole, high-density lipoprotein cholesterol (HDL), low-density lipoprotein cholesterol (LDL), triglyceride (TG), glucose, alanine aminotransferase (ALT), aspartate aminotransferase (AST), and creatinine were measured with an automatic analyzer (Hitachi Co., Tokyo, Japan).

Atherosclerotic lesion

Mice were anesthetized and euthanized after 16 weeks of WD or Con. The aortas were washed with phosphate-buffered saline (PBS) and then fixed with 10% paraformaldehyde overnight. The adventitia was cleaned thoroughly under a dissecting microscope, and fixed aortas were stained with Oil Red O stock solution (0.3% w/v in isopropyl alcohol) for 1 h

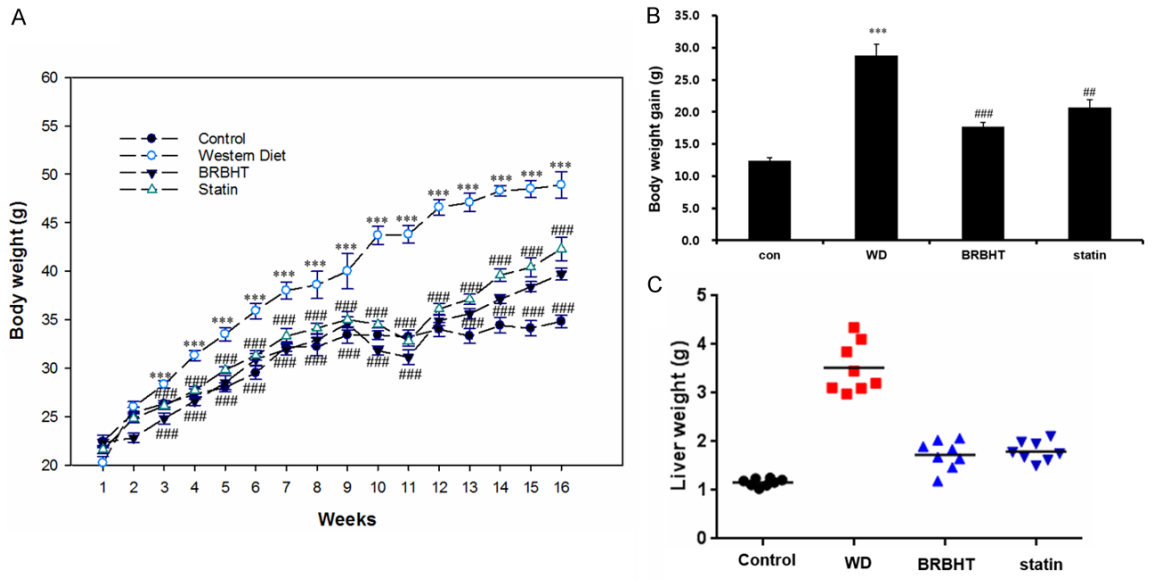

Figure 1. Effects of BRBHT in WD-induced ApoE KO mice. Mice (8 weeks old) were experiments were carried out for 16 weeks. (A) Body weight was measured every week for 16 weeks. (B) Body weight gain (C) After 16 weeks of ND or WD, liver tissues were collected and washed with cold phosphate-buffered solution, after which they were weighed. Values are mean ± SEM. $^{**}P < 0.01$, $^{***}P < 0.001$ vs. ND; $^{###}P < 0.001$ vs. WD. ApoE KO, ApoE Knockout; ND, Normal diet; WD, western diet; BRBHT, Bok Ryung Ban Ha -Tang.

Table 2. Effect of BRBHT on Liver weight in ApoE KO mice fed a WD

			BRBHT	*Atorvastatin*
	Con	WD	150 mg/kg	10 mg/kg
Liver weight (g)	1.16±0.08	3.57±0.21***	1.73±0.11$^{###}$	1.86±0.08$^{###}$

Metabolic characteristics were measured from ApoE KO mice fed a WD for 16 weeks. Abbreviations: ApoE KO, ApoE Knockout; WD, Western diet; BRBHT, Bok Ryung Ban Ha -Tang. Values are expressed as the mean ± SEM. n=8; $^{***}P < 0.001$, vs. *ApoE KO* mice without WD (Con; Normal diet). $^{###}P < 0.001$, vs. WD-fed *Apo KO* mice (WD).

and then destained in PBS containing 0.5% tween 20 for 48 min. Images were collected using a microscope.

Histopathology

Mice were deeply anesthetized with sodium thiopental and subsequently perfused with cold PBS, followed by fixation with 10% (w/v) paraformaldehyde overnight. Livers were embedded in paraffin and sectioned serially at 4 μm. The sections were stained with H&E. The steined sections were analysis by light microscopy (Olympus optical Co., Tokyo, Japan).

Data analysis

Values are expressed as the mean ± standard error of the mean (SEM). Statistical comparisons were performed using unpaired Student's t-tests and analysis of variance (ANOVA) for repeated measures followed by post hoc pairwise comparisons in SigmaPlot software version 13.0 (Systat Software Inc.; San Jose, CA, USA). Differences were considered significant at $P < 0.05$.

Results

Effect of BRBHT on body weight and liver weight in ApoE KO mice

To investigate BRBHT prossesses anti-atherosclerosis activites mice were fed with normal diet (Control; Con), WD or WD supplemented with BRBHT for 16 weeks, and their body weight monitored. After 3 weeks feeding, the WD group showed significantly increased body weight compared with that of the control ($P < 0.001$). BRBHT supplementation ameliorated the increased body weight of WD fed mice ($P < 0.001$; **Figure 1A**). As shown in **Figure 1B**, the body weight gain of the WD group was also increased compared to the control ($P < 0.001$), and the BRBHT suplementation attenuated this increased ($P < 0.001$). These results revealed that the supplementation of BRBHT

Table 3. Effect of BRBHT on Blood pressure in ApoE KO mice fed a WD

			BRBHT	*Atorvastatin*
	Con	WD	150 mg/kg	10 mg/kg
Blood pressure (mmHg)				
Mean pressure	93.0±1.30	117.0±5.48**	90.0±3.20##	98.0±3.25#
Diastolic	108.0±2.84	140.0±7.04**	107.0±3.59##	119.0±5.40#
Systolic	78.0±3.27	94.0±4.50*	74.0±3.00##	77.0±2.16##

Metabolic characteristics were measured from ApoE KO mice fed a WD for 16 weeks. Abbreviations: ApoE KO, ApoE Knockout; WD, western diet; BRBHT, Bok Ryung Ban Ha -Tang. Values are expressed as the mean ± SEM. n=8; ***P < 0.001, vs. *ApoE KO* mice without WD (Con; Normal diet). ###P < 0.001, vs. WD-fed *ApoE KO* mice (WD).

Table 4. Effect of BRBHT on Biochemical parameters in serum of ApoE KO mice fed a WD

			BRBHT	*Atorvastatin*
	Con	WD	150 mg/kg	10 mg/kg
T-chole (mg/dL)	479.00±28.32	1232.57±72.45***	929.71±33.74#	965.67±31.90#
LDL (mg/dL)	75.29±3.11	328.71±35.22***	250.57±15.05#	271.17±16.62
HDL (mg/dL)	19.43±2.14	12.14±1.64*	16.29±1.52	15.00±1.54
TG (mg/dL)	73.00±9.58	181.43±80.05	44.14±5.27#	89.83±12.99
Glucose (mg/dL)	202.29±18.73	376.57±72.57*	271.43±20.35#	240.50±32.77#
AST (U/L)	135.57±32.26	499.01±48.63***	289.14±21.92###	374.00±69.78
ALT (U/L)	72.00±19.37	413.43±75.48***	224.57±29.69#	313.33±76.23
Creatinine (mg/dL)	0.22±0.01	0.32±0.06	0.23±0.03	0.23±0.03

Metabolic characteristics were measured from ApoE KO mice fed a WD for 16 weeks. Abbreviations: ApoE KO, ApoE Knockout; WD, western diet; BRBHT, Bok Ryung Ban Ha -Tang; T-chole, total cholesterol; LDL, low-density lipoprotein; HDL, high-density lipoprotein; TG, triglyceride; AST, aspartate aminotransferase; ALT, alanine aminotransferase. Values are expressed as the mean ± SEM. n=8; ***P < 0.001, vs. *ApoE KO* mice without WD (Con; Normal diet). ###P < 0.001, vs. WD-fed *ApoE KO* mice (WD).

moderately attenuated the increased body weight of WD-fed mice. On the other hand, the liver weights are listed in **Table 2** and **Figure 1C**. The liver weight was higher in the WD group than in the Con group, However significantly lower by BRBHT.

Effect of BRBHT on blood pressure

we confirmed that *BRBHT* reduced blood pressure. During the course of the experiment, blood pressure in the WD group was significantly higher than that in the control group (117.0±5.48 vs. 93.0±1.30 mmHg, P < 0.01). In contrast, the blood pressure was significantly lower in the BRBHT groups (90.0±3.20 mmHg, P < 0.01) or in the Atorvastatin group (98.0±3.25 mmHg, P < 0.05). And, diastolic and systolic blood pressure was lower in the BRBHT or Atorvastatin (**Table 3**).

Effect of BRBHT on biochemical levels

The serum biochemical parameters are listed in **Table 4**. The serum levels of total cholesterol (P < 0.001), Glucose (P < 0.01), AST (P < 0.001) and AST (P < 0.001) were significantly elevated in mice fed WD compared with control group, were also significantly decreased (P < 0.001 and 0.05) by BRBHT or Atorvastatin (**Table 4**).

Effect of BRBHT on atherosclerotic lesions and hepatic steatosis

WD fed mice exhibited a uniformly pale fatty liver and hepatomegaly, and these pathological changes were reversed by BRBHT. Adiministreation of BRBHT eliminated excess fat accumulation in hepatic intracellular vacuoles, as determined by hematoxylin and eosin (H&E) and oli red o staining (**Figure 2A** and **2B**). Moreover, atheroslcortic lesion revealed fatty streak lesions in the aortic root of WE fed mice, indicating early development of ahteroscleroitc plaque. But, the elevated aortic root lesion was reduced by BRBHT (**Figure 2C**). These result indicated that, BRBHT effectively improves diet-induced atherosclerosis and hepatic steatosis.

Discussion

The Korean herbal medicine, BRBHT, has been shown to prevent liver steatosis responses and

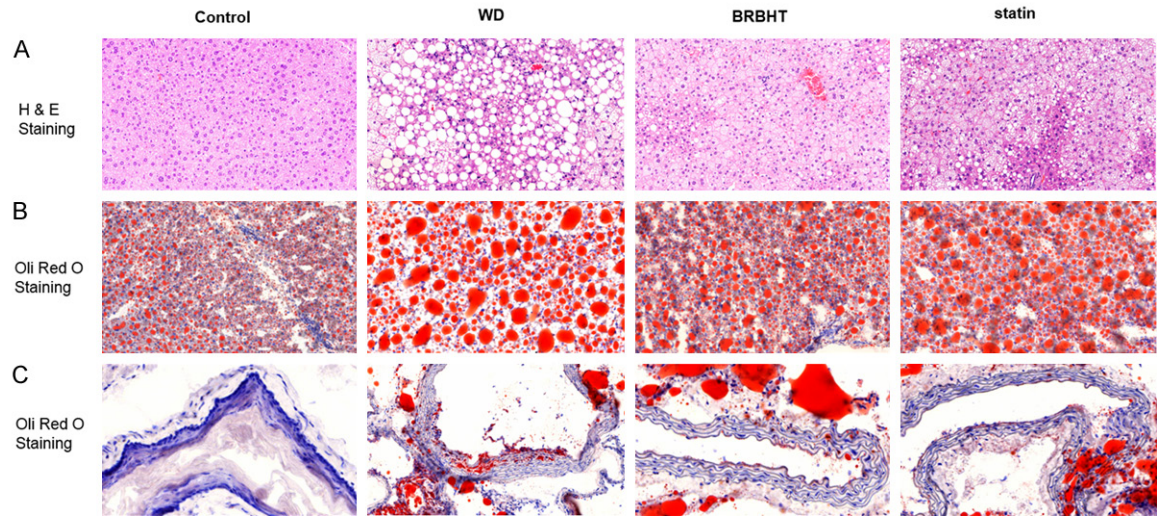

Figure 2. Effect of BRBHT on liver steatosis and atherosclerotic plaque in WD-induced ApoE KO mice. BRBHT was orally administered to mice at a dose of 150 mg/kg/day for 16 weeks. Representative images of (A) hematoxylin and eosin-stained sections (B) and oli red o of liver. (C) Oil red o stained of aorta. (magnification, ×100). ApoE KO, ApoE Knockout; WD, western diet; BRBHT, Bok Ryung Ban Ha -Tang.

lipid deposition in atherosclerosis mice. Currently, it is used to treat blood stasis by promoting blood circulation. In this study, we evaluated the anti-atherosclerotic properties of BRBHT.

The result of the present study demonstrated that BRBHT treatment reduced body weight, body weight gain, blood pressure, liver weight, and the serum levels of T-chole, LDL, TG, and glucose, in WD-fed ApoE KO mice, also AST, ALT were significantly chaged in the BRBHT mice compared with the levels in the WD mice. Moreover, Attenuation of the development of atherosclerotic lesions and reduced liver steatosis. These data show that BRBHT has potent hypolipidemic and anti-atherosclerosis effects. In addation, the BRBHT treatment no affect liver toxicity of BRBHT in rather due to a direct pharmacological action on the liver. These data suggest that BRBHT attenuates hypercholesterolemic atherosclerosis and this effect is associated with a decrease in serum lipid and liver steatosis.

High serum lipid levels, sepecially the elevated level of low-density lipoprotein (LDL), have been shown to ne strongly related to the development of atherosclerosis [13]. Therefore, lipid lowering therapy significantly reduces the risk of cardiovsscular disease such as atherosclerosis. In part, this improved outcome has been attributed to slowed progression of atherosclerosis consequent to a decrease in hypercholesterolemia [14]. Previous studies have suggested that ameliorated the progression of atheroma formationby significantly decreased total and LDL cholesterol levels in the entire aorta in ApoE KO mice fed the High fat diet [15]. In the present study, lipid levels resulted in significantly reduced T-chol, LDL, TG, Glucose levels bt BRBHT in ApoE KO mice fed WD with BRBHT compared ApoE KO mice fed WD. Presently, the BRBHT modulated plasma cholesterol level and it is possible that these effects may have inhibited atherosclerotic lesion and liver steatosis in ApoE KO mice fed WD.

BRBHT have been three species composed of *Pinellia ternata* (Thunb.) Breit, *Wolfiporia extensa*, *Zingiber officinale* approved for use. The three species composed are safe abd efficient in their wespective therapeutic categories with some different and similar action mechanisms. *Pinellia ternata* (Thunb.) Breit, which is a effectively inhibited TNF-a induced NF-κB activation and fatty acid as PPAR agonist being key regulators of gene involved in lipid and glucose metabolism [16]. *Wolfiporia extensa,* Many previous studies have indicated that its extracts and conponets have a variety of biological activities such as anto-hypertonic, anti-inflammatory, anti-angiogenic effects [17-19]. Moreover, Gei ji Bok ryung -Hwan (*Wolfiporia extensa*

composition) has been shown to reduced an atherosclerotic area in the abdominal aorta and prevent of endothelial damage/cholesterol deposition in the thoracic aorta of cholesterol-fed rabbits [20]. *Zingiber officinale* preferential effects on plasma lipids, reverse cholesterol transport, cholesterol synthesis and inflammatory status in hypercholesterolaemic rabbit [21]. It is likely that three drugs that possess similar mechanisms of action may result in an effective therapy. Results from these studies support our data and suggest that BRBHT reduced atherosclerotic lesions and cholesterol deposition, providing a potential strategy for preventing atherosclerosis.

In summary, BRBHT preventes atherosclerosis through reduced of atherosclerotic lesion and liver steatosis via regulated plasma levels. This finding may provide convincing evidence to support protective effects of BRBHT therapy on atherosclerosis and lipidemia without apparent toxic side effects markes BRBHT a promising candidate in the development of anti-atherosclerosis pharmacotherapy.

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Disclosure of conflict of interest

None.

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References

[1] Kleemann R, Verschuren L, van Erk MJ, Nikolsky Y, Cnubben NH, Verheij ER, Smilde AK, Hendriks HF, Zadelaar S, Smith GJ, Kaznacheev V, Nikolskaya T, Melnikov A, Hurt-Camejo E, van der Greef J, van Ommen B, Kooistra T. Atherosclerosis and liver inflammation induced by increased dietary cholesterol intake: a combined transcriptomics and metabolomics analysis. Genome Biol 2007; 8: R200.

[2] Branuwald E. Shattuck lecture--cardiovascular medicine at the turn of the millennium: triumphs, concerns, and opportunities. N Engl J Med 1997; 337: 1360-1369.

[3] Jeon US, Choi JP, Kim YS, Ryu SH, Kim YK. The enhanced expression of IL-17-secreting T cells during the early progression of atherosclerosis in ApoE-deficient mice fed on a western-type diet. Exp Mol Med 2015; 47: 1-9.

[4] Hollander W. Role of hypertension in atherosclerosis and cardiovascular disease. Am J Cardiol 1976; 38: 786-800.

[5] National Heart, Lung, and Blood Institute. How is atherosclerosis treated? National Institutes of Health (NIH) 2014.

[6] Lewington S, Whitlock G, Clarke R, Sherliker P, Emberson J, Halsey J, Qizilbash N, Peto R, Collins R. Blood cholesterol and vascular mortality by age, sex, and blood pressure: a meta-analysis of individual data from 61 prospective studies with 55,000 vascular deaths. Lancet 2007; 370: 1829-39.

[7] Mizranita V, Pratisto EH. Statin-associated ocular disorders: the FDA and ADRAC data. Int J Clin Pharm 2015; 37: 844-850.

[8] Song MY, Lv N, Kim EK, Kwon KS, Yoo YB, Kim JH, Lee SW, Song JH, Lee JH, Lee SK, Shin BC, Ryu DG, Park BH, Kwon KB. Antiobesity activity of aqueous extracts of Rhizoma Dioscoreae Tokoronis on high-fat diet-induced obesity in mice. J Med Food 2009; 12: 304-309.

[9] Yoon JJ, Lee YJ, Park OJ, Lee SM, Lee YP, Cho NG, Kang DG, Lee HS. Doinseunggitang ameliorates endothelial dysfunction in diabetic atherosclerosis. Evid Based Complement Alternat Med 2013; 783576: 1-10.

[10] Heo J. DongUiBoGam, 1613; Re-compilation (2011), DongUiBoGam Part1. Edited by Ahn SW. Internal Bodily Elements. Korea: Korea Institute of Oreintal Medicine; pp. 334.

[11] Kim JH, Park SH, Kim YW, Ha JM, Bae SS, Lee GS, Cho SI, Choi BT, Shin HK. The Traditional Herbal Medicine, Dangkwisoo-San, Prevents Cerebral Ischemic Injury through Nitric Oxide-Dependent Mechanisms. Evid Based Complement Alternat Med 2011; 718302: 1-8.

[12] Leuschner F, Panizzi P, Chico-Calero I, Lee WW, Ueno T, Cortez-Retamozo V, Waterman P, Gorbatov R, Marinelli B, Iwamoto Y, Chudnovskiy A, Figueiredo JL, Sosnovik DE, Pittet MJ, Swirski FK, Weissleder R, Nahrendorf M. Angiotensin-converting enzyme inhibition prevents the release of monocytes from their splenic reservoir in mice with myocardial infarction. Circ Res 2010; 107: 1364-1373.

[13] Choy PC, Siow YL, Mymin D, O K. Lipids and atherosclerosis. Biochem Cell Biol 2004; 82: 212-224.

[14] Tarchalski J, Guzik P, Wysocki H. Correlation between the extent of coronary atherosclerosis and lipid profile. Mol Cell Biochem 2003; 246: 25-30.
[15] Sekiya M, Funada J, Watanabe K, Miyagawa M, Akutsu H. Effects of probucol and cilostazol alone and in combination on frequency of poststenting restenosis. Am J Cardiol 1998; 82: 144-147.
[16] Rozema E, Atanasov AG, Fakhrudin N, Singhuber J, Namduang U, Heiss EH, Reznicek G, Huck CW, Bonn GK, Dirsch VM, Kopp B. Selected Extracts of Chinese Herbal Medicines. Their Effect on NF-κB, PPARα and PPARγ and the Respective Bioactive Compounds. Evid Based Complement Alternat Med 2012; 983023: 1-10.
[17] Jeong JW, Lee HH, Han MH, Kim GY, Hong SH, Park C, Choi YH. Ethanol extract of Poria cocos reduces the production of inflammatory mediators by suppressing the NF-kappaB signaling pathway in lipopolysaccharide-stimulated RAW 264.7 macrophages. BMC Complement Altern Med 2014; 14: 1-8.
[18] Lee SM, Lee YJ, Yoon JJ, Kang DG, Lee HS. Effect of Poria cocos on hypertonic stress-induced water channel expression and apoptosis in renal collecting duct cells. J Ethnopharmacol 2012; 141: 368-376.
[19] Rios JL. Chemical constituents and pharmacological properties of *Poria cocos*. Planta Med 2011; 77: 681-691.
[20] Kim BJ, Kim YK, Park WH, Ko JH, Lee YC, Kim CH. A water-extract of the Korean traditional formulation Geiji-Bokryung-Hwan reduces atherosclerosis and hypercholesteremia in cholesterol-fed rabbits. Int Immunopharmacol 2003; 3: 723-734.
[21] Elseweidy MM, Younis NN, Elswefy SE, Abdallah FR, El-Dahmy SI, Elnagar G, Kassem HM. Atheroprotective potentials of curcuminoids against ginger extract in hypercholesterolaemic rabbits. Nat Prod Res 2015; 10: 961-965.