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Effects of Black Raspberry on Lipid Profiles and Vascular Endothelial Function in Patients with Metabolic Syndrome

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Black raspberry (*Rubus occidentalis*) has been known for its anti-inflammatory and anti-oxidant effects. However, short-term effects of black raspberry on lipid profiles and vascular endothelial function have not been investigated in patients with metabolic syndrome. Patients with metabolic syndrome ($n = 77$) were prospectively randomized into a group with black raspberry ($n = 39$, 750 mg/day) and a placebo group ($n = 38$) during a 12-week follow-up. Lipid profiles, brachial artery flow-mediated dilatation (baFMD), and inflammatory cytokines such as IL-6, TNF-α, C-reactive protein, adiponectin, sICAM-1, and sVCAM-1 were measured at the baseline and at the 12-week follow-up. Decreases from the baseline in the total cholesterol level (−22.8 ± 30.4 mg/dL vs. −1.9 ± 31.8 mg/dL, $p < 0.05$, respectively) and total cholesterol/HDL ratio (−0.31 ± 0.64 vs. 0.07 ± 0.58, $p < 0.05$, respectively) were significantly greater in the group with black raspberry than in the placebo group. Increases in baFMD at the 12-week follow-up were significantly greater in the group with black raspberry than in the placebo group (0.33 ± 0.44 mm vs. 0.10 ± 0.35 mm, $p < 0.05$, respectively). Decreases from the baseline in IL-6 (−0.4 ± 1.5 pg/mL vs. −0.1 ± 1.0 pg/mL, $p < 0.05$, respectively) and TNF-α (−2.9 ± 4.7 pg/mL vs. 0.1 ± 3.6 pg/mL, $p < 0.05$, respectively) were significantly greater in the group with black raspberry. The use of black raspberry significantly decreased serum total cholesterol level and inflammatory cytokines, thereby improving vascular endothelial function in patients with metabolic syndrome during the 12-week follow-up.

Keywords: black raspberry; metabolic syndrome; lipid; endothelial function; inflammation.

INTRODUCTION

Black raspberry (*Rubus occidentalis*) is a member of the Rosaceae family and grows wild in South Korea, Japan, and China. Black raspberry has been used to treat prostate and urinary diseases in Korea (Kim *et al*., 2005). The extract of this plant contains large amounts of various natural components such as flavonoids, tannins, phenolic acids, organic acids, tyrosol, and resveratrol (Wang and Lin, 2000). These pharmaceutically active components have anti-inflammatory, anti-oxidative, and anti-atherosclerotic effects by inhibiting the formation of activated oxygen molecules and increasing inducible nitric oxide synthase (iNOS) and endothelial nitric oxide synthase (eNOS) (Lim *et al*., 2012; Wallerath *et al*., 2002; Yang *et al*., 2008; Zhao *et al*., 2011). The components of tyrosol and resveratrol reduce the uptake of oxidized low-density lipoprotein (LDL) by monocytes/macrophages through the regulation of JNK activation (Bhandary *et al*., 2012; Vivancos and Moreno, 2008). Resveratrol has been demonstrated to promote vasodilation, prevent the oxidation of LDL-cholesterol, and inhibit cholesterol synthesis as polyphenolic compounds (Chen and Pace-Asciak, 1996; Ou *et al*., 2006; Rakici *et al*., 2005). The inhibition of the uptake of oxidized LDL is one of the major therapeutic targets of atherosclerosis (Rader and Daugherty, 2008).

The components of metabolic syndrome constitute significant cardiovascular risk factors such as dyslipidemia, insulin resistance, and inflammation, thereby contributing to atherogenicity (Opie, 2007). However, no prospective randomized study has examined the effects of black raspberry during the early stages of atherosclerosis in high-risk patients. In this regard, the present study investigates the short-term effects of black raspberry on lipid profiles and vascular endothelial function in patients with metabolic syndrome.

MATERIALS AND METHODS

Study patients. Patients were eligible for this study if they were between 18 and 75 years old with metabolic syndrome. For patients with metabolic syndrome, ≥3 of the following measurements have to be fulfilled: abdominal circumference ≥90 cm in men or ≥85 cm in women, triglyceride level ≥150 mg/dL, high-density lipoprotein (HDL) cholesterol <40 mg/dL in men or <50 mg/dL in women, systolic blood pressure ≥130 mm

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Hg, diastolic blood pressure ≥85 mm Hg, and fasting blood glucose ≥100 mg/dL.

A total of 152 patients with metabolic syndrome were screened for their inclusion in the study at the Korea University Anam Hospital Cardiovascular Center from March 2013 through July 2013. Patients who did not fulfill the inclusion criteria ($n = 6$) and who did not provide informed consent ($n = 52$) were excluded. In addition. We excluded patients ($n = 17$) with familial hypercholesterolemia; hepatic dysfunction (aspartate aminotransferase or alanine aminotransferase >twice the upper limit); gastrointestinal disorders such as Crohn's disease; a history of surgery, alcohol abuse, or steroid or hormone replacement therapy; serum creatinine >2.0 mg/dL; or expected life expectancy <1 year (Fig. 1). Eligible patients ($n = 77$) were prospectively randomized into a group with black raspberry ($n = 39$, 750 mg/day equivalent of 4 capsules/day) and a placebo group ($n = 38$) during the 12-week follow-up. Dried unripe black raspberries were made into powder, and capsules of the powder were produced under good manufacturing practices. Each capsule contained 187.5 mg of the powder. Placebo capsules had the same appearance but contained cellulose, isomalto, and corn powder.

A complete clinical workup was scheduled at the baseline and the 12-week follow-up. Lipid profiles, including total cholesterol, triglyceride, HDL cholesterol, LDL cholesterol, lipoprotein(a), apolipoprotein A-I, apolipoprotein B, and their ratios, were compared between the two groups. Inflammatory markers such as interleukin (IL)-6, the tumor necrosis factor (TNF)-α, high-sensitive C-reactive protein (hsCRP), adiponectin, soluble intercellular adhesion molecule-1 (sICAM-1), soluble vascular cell adhesion molecule-1 (sVCAM-1), brachial artery flow-mediated dilatation (baFMD), and carotid intima-media thickness (IMT) were compared between the two groups during the follow-up. The primary endpoints of the study were to compare the short-term effects of black raspberry on lipid profiles and vascular endothelial function in patients with metabolic syndrome during the 12-week follow-up. The study was approved by the University Hospital Institute Review Board, and written informed consent was obtained from all participants or their legal guardians.

Preparation of the unripe *R. occidentalis* extract. Unripe fruits of *R. occidentalis* were collected from the Gochang (Jeollabuk-Do) area in South Korea. Briefly, the fruits were extracted twice with tap water at 100 °C by using a reflux condenser, and extracts were filtered and concentrated. Concentrates were lyophilized in a freeze dryer. Ellagic acid was used as a marker compound to develop a suitable identification test for raw materials.

Brachial artery flow-mediated dilatation measurement. The diameter of the artery was measured using a high-frequency ultrasound machine (Vivid 7, GE Vingmed Ultrasound, Horten, Norway) with a 10-MHz linear-array transducer. ECG-gated, vessel end-diastole B-mode images were analyzed. An experienced physician took all measurements for all subjects by using the same investigation protocol and techniques to reduce inter- and intra-observer variability. After a satisfactory transducer position was found, the antecubital fossa was marked, and the arm stayed in that position throughout the examination. After a 10-min rest in the supine position, the left brachial artery was identified longitudinally. After recording the resting brachial artery diameter, a cuff was placed around the forearm distal to the target artery and inflated to a pressure of 250 mm Hg. Inflation was maintained for 5 min. Endothelium-dependent vasodilation was assessed by measuring the change in the diameter of the brachial artery 60 s of reactive hyperemia relative to baseline measurements after the deflation of the cuff placed around the forearm. After baseline conditions were reestablished 15 min later, brachial artery measurement was repeated, and the measurements were averaged.

Measurement of carotid intima-media thickness. Carotid ultrasound measurements were obtained at the baseline

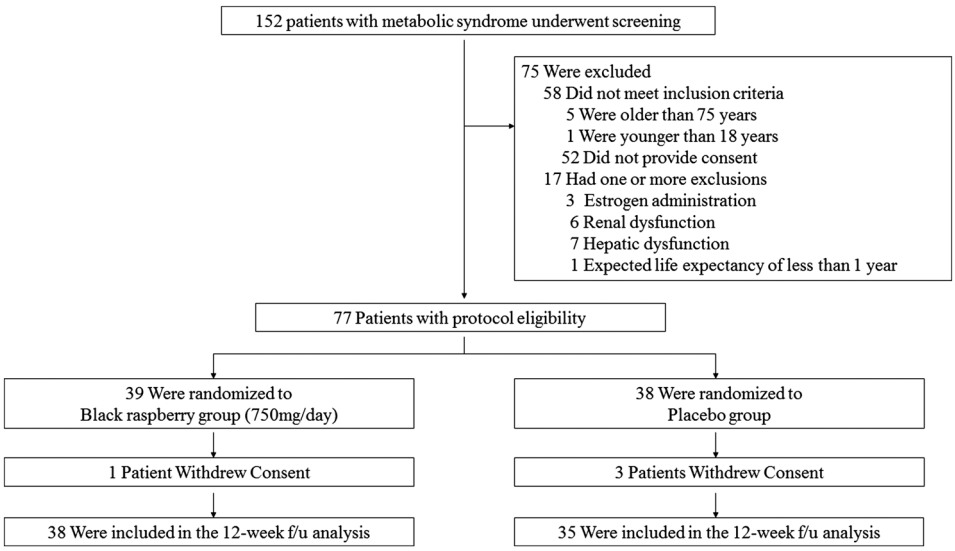

Figure 1. Study protocol. Patients with metabolic syndrome (n = 77) were prospectively randomized into the black raspberry group (n = 39, 750 mg/day), and placebo group (n = 38).

and 12 weeks after randomization. Imaging studies of the left and right carotid arteries were conducted using a 10-MHz linear vascular probe (Vivid 7, GE Vingmed Ultrasound, Horten, Norway). Standardized longitudinal B-mode images were obtained from near and far walls of common, external, and internal carotid arteries. The common carotid artery was defined as the segment extending from 10 to 20 mm proximal to the tip of the bifurcation site of the common carotid. Internal and external carotid arteries were defined as the segment 10 mm distal to the tip of the bifurcation site of the common carotid. The maximum IMT was defined as the mean of the maximum IMT of the near and far walls of the common, internal, and external carotid arteries on both the left and right sides. The carotid IMT was measured using dedicated software (IntimaScope, Media Cross Co., Tokyo, Japan) by a reader blinded to all clinical information.

Pulse wave velocity and ankle brachial index measurements. All patients were evaluated for the brachial-ankle pulse wave velocity (baPWV) at the baseline and the 12-week follow-up. After a subject rested in a supine position for 5 min, baPWV was measured using a volume-plethysmographic apparatus (model BP-203RPE II; Colin, Komaki, Japan). This instrument simultaneously records baPWV and brachial and ankle blood pressure on the left and right sides. Changes from the baseline in the left and right baPWV were compared between the two groups during the follow-up. The ankle brachial index (ABI) was measured by determining systolic pressure in the brachial artery and in both the dorsalis pedis and posterior tibial arteries. The systolic pressure of each leg was divided by brachial pressure.

Laboratory analysis. Inflammatory markers such as hsCRP, IL-6, and TNF-α were measured for both groups at the beginning of the study and at the 12-week follow-up visit. Venous blood samples were drawn from each patient after 8 h or overnight fasting. Blood samples were centrifuged to obtain plasma, which was stored at −80 °C. TNF-α was measured by a sandwich enzyme-linked immunosorbent assay (ELISA) with a minimum detectable level of 0.5 pg/mL (ALPCO Diagnostics, Salem, NH, USA). Undetectable TNF-α values were recorded as 0.4 pg/mL. High-sensitivity IL-6 was measured by a sandwich ELISA with a minimum detectable level of 0.16 pg/mL (ALPCO Diagnostics, Salem, NH, USA). hsCRP concentration was quantified using the latex nephelometer II (Dade Behring Inc., Newark, DE, USA). The plasma adiponectin concentration was assessed by radioimmunoassay (Linco Research, Inc. St. Charles, MO, USA). The sensitivity of this assay was 0.78 ng/mL. The coefficients of variation for intra- and interassay were 9.3 and 15.3%, respectively. In addition, sICAM-1 and sVCAM-1 were measured using ELISA according to the manufacturer's instructions (R&D Systems, Minneapolis, Minnesota, USA).

Total cholesterol, triglyceride, HDL cholesterol, and LDL cholesterol levels were determined by enzymatic methods using standard biochemical procedures on the B.M. Hitachi 747 automated clinical chemistry analyzer (Hitachi, Tokyo, Japan). Plasma glucose was measured using the glucose oxidase method.

Statistical analysis. Data were expressed as means for continuous variables, and data for the categorical variables are expressed as the number and the percentage of patients. The chi-square test was conducted for categorical variables. Changes from the baseline were calculated as the value obtained at the end of the treatment subtracted from the value obtained at the beginning of the study. The results between two groups were compared by unpaired Student's *t*-test, and comparisons between before and after the treatment were analyzed by a paired *t*-test. Based on a two-sided test for differences in independent binomial proportions with an α level of 0.05, we calculated that 60 patients (30 patients in each group) had to undergo randomization for the study to have 80% power to detect a difference in the lipid profile between the two groups, and therefore, 77 patients in each group were enrolled to account for a 20% loss in the 12-week follow-up. Variables without a normal distribution were log-transformed in the subsequent analysis. $P < 0.05$ was considered statistically significant. SPSS (version 20.0) was used for the analysis.

RESULTS

Patient characteristics

Baseline patient characteristics such as the mean age and the body mass index were similar between the two groups (Table 1). Risk factors such as hypertension, diabetes, hyperlipidemia, and current smoking did not show significant differences between the two groups. In addition, there was no significant difference in medication at the baseline between the two groups (Table 1).

Changes in lipid profiles

Decreases from the baseline in the total cholesterol level (−22.8 ± 30.4 mg/dL vs. −1.9 ± 31.8 mg/dL, $p < 0.05$, respectively) and the total cholesterol/HDL ratio (−0.31 ± 0.64 vs. 0.07 ± 0.58, $p < 0.05$, respectively) were significantly greater in the group with black raspberry than in the placebo group (Table 2). Although a significant decrease in LDL cholesterol was observed only in the group with black raspberry during the 12-week follow-up, changes from the baseline showed no significant differences between the two groups (Table 2).

Brachial artery flow-mediated dilatation and aortic stiffness

Changes in baFMD at the baseline were similar between the two groups (0.27 ± 0.23 mm vs. 0.27 ± 0.23 mm, $p = 0.991$). However, increases in baFMD at the 12-week follow-up were significantly greater in the group with black raspberry than in the placebo group (0.33 ± 0.44 mm vs. 0.10 ± 0.35 mm, $p < 0.05$, respectively)

Table 1. Baseline patient characteristics

Variable	Black raspberry (n = 39)	Placebo (n = 38)	P value
Age (yrs)	58.0 ± 9.2	60.1 ± 9.5	0.313
Men	19 (48.7%)	17 (44.7%)	0.726
Height (m)	1.62 ± 0.08	1.62 ± 0.09	0.875
Weight (kg)	69.5 ± 15.4	65.7 ± 12.7	0.247
Body mass index (kg/m^2)	26.3 ± 4.3	25.1 ± 4.0	0.187
Waist (cm)	84.2 ± 8.1	81.2 ± 6.8	0.090
Risk Factors			
Hypertension	26 (66.7%)	20 (52.6%)	0.209
Diabetes	8 (20.5%)	5 (13.2%)	0.389
Hyperlipidemia	13 (33.3%)	13 (34.2%)	0.935
Smoker	6 (15.4%)	4 (10.5%)	0.526
Alcohol	15 (40.5%)	16 (42.1%)	0.891
Medications at baseline			
Aspirin	8 (20.5%)	7 (18.4%)	0.817
Clopidogrel	7 (17.9%)	6 (15.8%)	0.800
ACE inhibitor	3 (7.7%)	4 (10.5%)	0.711
ARB	15 (38.5%)	17 (44.7%)	0.576
Beta blocker	5 (12.8%)	4 (10.5%)	1.000
Calcium channel blocker	14 (35.9%)	12 (31.6%)	0.689
Diuretics	3 (7.7%)	3 (7.9%)	1.000
Statin	13 (33.3%)	14 (36.8%)	0.747

(Table 3). However, left and right baPWV, ABI, and IMT did not differ significantly between the two groups during the follow-up (Supplemental Tables 1 and 2).

Changes in inflammatory parameters during the 12-week follow-up

Decreases from the baseline in IL-6 (−0.4 ± 1.5 pg/mL vs. −0.1 ± 1.0 pg/mL, $p < 0.05$, respectively) and TNF-α (−2.9 ± 4.7 pg/mL vs. 0.1 ± 3.6 pg/mL, $p < 0.05$, respectively) were significantly greater in the group with black raspberry than in the placebo group (Table 4). Increases from the baseline in adiponectin levels (2.0 ± 1.9 μg/mL vs. 0.1 ± 2.0 μg/mL, $p < 0.05$, respectively) were significantly greater in the group with black raspberry. However, changes in hsCRP levels were similar between the two groups (Table 4).

DISCUSSION

This is the first prospective randomized double-blind study investigating the effects of black raspberry on lipid profiles and vascular endothelial function. Administering black raspberry (*R. occidentalis*) 750 mg/day for 12 weeks led to significant decreases in total cholesterol and inflammatory markers such as IL-6 and TNF-α and significant increases in adiponectin levels, thereby contributing to improvements in baFMD in this study. Some abnormality of baFMD indicates endothelial dysfunction, which can occur in the early stages of atherosclerosis progression (Celermajer *et al.*, 1992), and increases in total and LDL cholesterol with inflammatory markers expedite atherosclerosis progression. Although the administration of black raspberry did not reveal significant

Table 2. Changes in lipid profiles

Variable	Black raspberry (n = 39)		Placebo (n = 38)	
	Baseline	12-week F/U	Baseline	12-week F/U
Total cholesterol (mg/dL)	198.7 ± 34.0	174.7 ± 30.0*†	193.1 ± 30.1	189.7 ± 29.3
Changes from baseline (mg/dL)	−22.8 ± 30.4†		−1.9 ± 31.8	
Triglyceride (mg/dL)‡	152.1 ± 43.9	160.9 ± 58.9	126.9 ± 67.6	141.5 ± 59.9
Changes from baseline (mg/dL)	12.7 ± 51.7		13.1 ± 62.5	
HDL-cholesterol (mg/dL)	50.8 ± 12.5	48.3 ± 11.1*	54.5 ± 12.6	51.9 ± 9.8*
Changes from baseline (mg/dL)	−2.5 ± 6.8		−2.6 ± 7.0	
LDL-cholesterol (mg/dL)	98.0 ± 19.4	88.2 ± 20.9*	96.6 ± 17.6	94.8 ± 17.2
Changes from baseline (mg/dL)	−9.3 ± 20.8		−0.2 ± 18.6	
Lipoprotein (a) (mg/dL)	17.1 ± 17.0	16.5 ± 17.6	23.9 ± 22.0	22.9 ± 24.2
Changes from baseline (mg/dL)	−1.0 ± 5.0		−1.5 ± 5.6	
Apolipoprotein A-I (mg/dL)	141.2 ± 22.5	135.7 ± 21.3	135.0 ± 18.7	136.2 ± 16.6
Changes from baseline (mg/dL)	−5.4 ± 17.1		0.0 ± 9.4	
Apolipoprotein B (mg/dL)	91.4 ± 21.5	92.5 ± 19.8	93.2 ± 15.0	91.5 ± 17.7
Changes from baseline (mg/dL)	2.0 ± 16.5		−0.6 ± 17.0	
LDL/HDL ratio	2.01 ± 0.54	1.88 ± 0.54	1.86 ± 0.53	1.90 ± 0.46
Changes from baseline	−0.13 ± 0.43		0.05 ± 0.34	
Triglyceride/HDL ratio	3.13 ± 1.10	3.59 ± 1.72*	2.63 ± 2.01	3.00 ± 1.76
Changes from baseline	0.51 ± 1.21		0.27 ± 1.42	
Total cholesterol/HDL ratio	4.04 ± 0.83	3.75 ± 0.83*	3.68 ± 0.89	3.75 ± 0.81
Changes from baseline	−0.31 ± 0.64†		0.07 ± 0.58	
Apolipoprotein B/A-I ratio	0.66 ± 0.18	0.69 ± 0.18	0.71 ± 0.17	0.69 ± 0.17
Changes from baseline	0.04 ± 0.16		−0.01 ± 0.12	

*$p < 0.05$ compared with baseline.
†$p < 0.05$ compared with the placebo group.

Table 3. Changes in flow-mediated dilation during 12-week follow-up

Variables	Black raspberry (n = 39)		Placebo (n = 38)	
	Resting	Reactive hyperemia	Resting	Reactive hyperemia
Baseline				
Brachial artery diameter (mm)	4.08 ± 0.59	4.36 ± 0.60	3.93 ± 0.71	4.19 ± 0.74
Changes in diameter (mm)	0.27 ± 0.23		0.27 ± 0.23	
12-week follow-up				
Brachial artery diameter (mm)	3.75 ± 0.68	4.08 ± 0.79	3.92 ± 0.72	4.02 ± 0.74
Changes in diameter (mm)	0.33 ± 0.44 †		0.10 ± 0.35	

*$p < 0.05$ compared with baseline.
†$p < 0.05$ compared with the placebo group.

Table 4. Changes in inflammatory parameters during 12-week follow-up

Variables	Black raspberry (n = 39)		Placebo (n = 38)	
	Baseline	12-week follow-up	Baseline	12-week follow-up
IL-6 (pg/mL)‡	1.3 ± 1.0	0.9 ± 0.5*†	1.4 ± 1.4	1.3 ± 1.1
Changes from baseline (pg/mL)	−0.4 ± 1.5†		−0.1 ± 1.0	
TNF-α (pg/mL)‡	16.6 ± 3.3	13.6 ± 4.1*†	15.1 ± 5.6	15.3 ± 5.5
Changes from baseline (pg/mL)	−2.9 ± 4.7†		0.1 ± 3.6	
C-reactive protein (mg/L)	1.4 ± 1.5	1.1 ± 1.6	2.0 ± 2.6	1.4 ± 1.9
Changes from baseline (mg/L)	−0.3 ± 1.4		−0.6 ± 3.2	
Adiponectin (μg/mL)‡	5.7 ± 5.1	7.7 ± 5.0*†	6.1 ± 6.0	6.2 ± 6.4
Changes from baseline (μg/mL)	2.0 ± 1.9†		0.1 ± 2.0	
sICAM-1 (ng/mL)‡	415 ± 178	445 ± 230	438 ± 201	460 ± 198
Changes from baseline (ng/mL)	31 ± 92		21 ± 99	
sVCAM-1 (ng/mL)‡	980 ± 402	1021 ± 387	1050 ± 402	1055 ± 434
Changes from baseline (ng/mL)	40 ± 293		5 ± 389	

*$p < 0.05$ compared with baseline.
†$p < 0.05$ compared with placebo group.

changes in established aortic stiffness (Supplemental Table 1) and carotid intima-media thickness (Supplemental Table 2) during the relatively short-term follow-up, this study highlights that black raspberry could be effectively used to improve endothelial dysfunction in patients with metabolic syndrome with high risk factors for cardiovascular diseases.

The formation of oxLDL and oxidative stress has been understood to have a critical role in atherosclerosis (Stocker and Keaney, 2004). The uptake of oxLDL stimulates macrophages to form foam cells, eliciting the development of fibrous and atheromatous plaques (Ouimet and Marcel, 2012). Increased oxLDL levels are associated with increased IMT and impaired baFMD in asymptomatic subjects. Administering black raspberry reduced serum total cholesterol and LDL cholesterol levels in this study, thereby theoretically reducing the formation of oxLDL in atheromatous plaque (Gerber *et al.*, 2013). Activated macrophages secrete inflammatory cytokines, including IL-1β, IL-6, and TNF-α (Bosca *et al.*, 2005; Lawrence *et al.*, 2002). Excessive inflammatory cytokines may lead to tissue damage, reduce NO bioavailability, and increase the production of reactive oxygen species (ROS). The ROS directly reduces NO activity and modifies the expression of iNOS (Stocker and Keaney, 2004). Reduced serum IL-6 and TNF-α levels would increase NO bioavailability with improvements in baFMD in the group with black raspberry in this study. Decreased NO bioavailability upregulates sVCAM-1 which binds monocytes and lymphocytes to the endothelium. No significant differences in sVCAM-1 and sICAM-1 were noted in this study, probably because of the short duration of the follow-up for the downstream expression of adhesion molecules (Vasilev *et al.*, 2013). The CRP produced in vascular smooth muscle cells can directly participate in the atherosclerosis process by mediating monocyte recruitments and by stimulating monocytes to release IL-1, IL-6, and TNF-a (Verma *et al.*, 2006). However, no significant changes in hsCRP levels were found between the two groups during the follow-up. We speculate that hsCRP levels are affected by various factors in addition to IL-6 and TNF-α; therefore, we suggest that endothelial dysfunction may be reflected more prominently in upstream inflammatory markers such as IL-6 and TNF-α. On the other hand, a direct anti-atherosclerotic effect of adiponectin on endothelial function was found in the group with black raspberry based on decreasing inflammatory cytokines and ultimately interfering with TNF-α signaling.

Black raspberry contains high levels of ascorbic acid, anthocyanins, flavonoids, phenolic acids, organic acids, tyrosol, and resveratrol. It is also rich in tannins, pectin, B-carotene, catechin, epicatechin, and vitamins A, B1,

C, and E (Kong *et al*., 2003; Wang and Lin, 2000). Ascorbic acid, a fruit component, has the capacity to inhibit H_2O_2 free radical activity and thus has a strong antioxidant effect (Wang and Jiao, 2000). Anthocyanin is one of the most abundant phenolic compounds and possesses an antioxidant capacity (Seeram and Nair, 2002). Extract of the blackberry has a potential anti-inflammatory and anti-oxidant effect in in-vitro study (Azofeifa *et al*., 2013). The strong antioxidant activity of black raspberries corresponds to the high anthocyanin and phenolic content of this fruit (Viljanen *et al*., 2004). Anthocyanins possess anti-oxidant activity, anti-inflammatory effects, prevent LDL oxidation, and inhibit platelet aggregation (Demrow *et al*., 1995; Shafiee *et al*., 2003). The components of tyrosol and resveratrol have been demonstrated to lower oxygenated LDL uptake (Bhandary *et al*., 2012; Vivancos and Moreno, 2008). Resveratrol also promotes vasodilation and inhibits cholesterol synthesis (Chen and Pace-Asciak, 1996; Ou *et al*., 2006; Rakici *et al*., 2005). In addition, catechin has an anti-inflammatory effect by reducing the expression of IL-6 and IL-8 (Nakanishi *et al*., 2010). Further, flavonoids in black raspberry improve endothelium-dependent, flow-mediated vasodilation in patients with endothelial dysfunction (Stein *et al*., 1999). Therefore, black raspberry may contribute to improvements in endothelial dysfunction by inhibiting cholesterol synthesis and promoting antioxidant effects, anti-inflammatory effects, and vasodilation.

This study has some limitations. This is the first prospective, randomized, double-blind trial to investigate the effects of black raspberry on lipid profiles and endothelial dysfunction in high-risk patients. However, the total number of study participants was relatively small for the evaluation of clinical cardiovascular events. Black raspberry contains various types of beneficial natural compounds such as polyphenolic compounds, but exact mechanisms underlying the relationship between beneficial compounds of black raspberry and favorable effects on lipid profiles and endothelial dysfunction should be further investigated.

In conclusion, the use of black raspberry significantly decreased serum total cholesterol levels and inflammatory cytokines, thereby improving vascular endothelial function in patients with metabolic syndrome during the 12-week follow-up.

Acknowledgement

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Conflict of Interest

There is no conflict of interest in connection with any commercial associations, and all authors have nothing to disclose.

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