Nutrition Research and Practice (*Nutr Res Pract*) 2011;5(5):429-434
http://dx.doi.org/10.4162/nrp.2011.5.5.429

Effects of a *Rubus coreanus* Miquel supplement on plasma antioxidant capacity in healthy Korean men

Ji Eun Lee[1], Eunkyo Park[1], Jung eun Lee[1], Joong Hyuck Auh[2], Hyung-Kyoon Choi[3], Jaehwi Lee[3], SooMuk Cho[4] and Jung-Hyun Kim[1§]

[1]*Department of Home Economics Education, Chung-Ang University, Heuksuk-dong, Dongjak-gu, Seoul 156-756, Korea*
[2]*Department of Food Science & Technology, Chung-Ang University, Gyeonggi 456-756, Korea*
[3]*College of Pharmacy, Chung-Ang University, Seoul 156-756, Korea*
[4]*Functional Food & Nutrition Division, Rural Development Administration, Gyeonggi 441-853, Korea*

Abstract

Korean raspberry, *Rubus coreanus* Miquel (RCM), contains high concentrations of phenolic compounds, which prevent oxidative stress. To determine the effect of RCM on antioxidant capacity in humans, we assessed *in vivo* lipid oxidation and antioxidant enzyme activities from plasma in 15 healthy men. The subjects ingested 30 g of freeze-dried RCM daily for 4 weeks. Blood was taken at baseline and at the end of the study to determine blood lipid profiles, fasting plasma glucose, liver function, lipid peroxidation, and antioxidant enzyme activities. RCM supplementation had no effect on blood lipid or fasting plasma glucose concentrations but decreased alkaline phosphatase activity. RCM supplementation increased glutathione peroxidase activities ($P < 0.05$) but had no effect on lipid peroxidation. These results suggest that short-term RCM supplementation may offer health benefits by enhancing antioxidant capacity in a healthy population.

Key Words: *Rubus coreanus* Miquel, antioxidant, lipid peroxidation, glutathione peroxidase

Introduction

Diets rich in fruits and vegetables protect against various chronic diseases such as cardiovascular diseases, stroke, and cancers [1-3]. These beneficial effects have been attributed to high concentrations of antioxidants such as vitamin C, vitamin E, carotenoids, and flavonoids [3-5]. Several epidemiological studies have reported that vitamin supplements or a high intake of fruits such as strawberries or blueberries increases plasma antioxidant capacity and lowers the risk for cardiovascular diseases [2,6,7]. However, other studies have shown that antioxidant supplements or a high intake of vegetables or fruits did not improve antioxidant capacity in healthy subjects [8,9]. These results suggest that different types of supplements or antioxidants could differentially affect the antioxidant system in humans.

The Korean raspberry, *Rubus coreanus* Miquel (RCM), has been used as a traditional remedy for liver and kidney diseases, spermatorrhoea, prostate and urinary disease, and allergic diseases [10-12]. Scientists have elucidated the active components in RCM and found that it contains various antioxidants such as polyphenols, tannins, phenolic acids, organic acids, triterpenoids, flavonoids, gallotannin, ellagitannin, and anthocyanins [13-15]. Several studies have shown that an RCM extract has higher electron donation ability and prevents low-density lipoprotein (LDL) oxidation in *in vitro* studies [14-16]. Other studies have shown that a ripened RCM extract decreases gastric tumor growth and stimulates osteoblastic cell proliferation and differentiation [17,18].

RCM has traditionally been used as a Oriental medicine, and recent studies have demonstrated its antioxidant, anti-tumorigenic, and anti-inflammatory effects in *in vitro* studies [14-17]. These effects might be related to the antioxidants. Thus, we determined the antioxidant effect of RCM on healthy human subjects.

Subjects and Methods

Subjects

Fifteen healthy participants were recruited with an age range of 20-30 years, and all participants completed the study. None of the participants had a history of cardiovascular disease, diabetes, or renal or liver disease but had not taken vitamin/mineral supplements or any other functional food during this

This research was financially supported by the Rural Development Administration (project number, PJ0063872010), and we sincerely appreciate the support.
§ **Corresponding Author:** Jung-Hyun Kim, Tel. 82-2-820-5378, Fax. 82-2-817-7304, Email. jjhkim@cau.ac.kr
Received: November 16, 2010, Revised: January 26, 2011, Accepted: January 26, 2011

study. The procedures used were in accordance with the institutional guidelines and approved by the Chung-Ang University Institutional Review Board (Seoul, South Korea). Informed consent was obtained from all study participants before starting the study.

Study protocol and analysis

RCM was obtained from the Rural Development Administration and RCM supplements were prepared by Herbcure (Pocheon, Korea) (Table 1). Subjects consumed supplements containing 30 g of freeze-dried RCM per day for 4 weeks. After overnight fasting, blood samples were collected by venipuncture into evacuated tubes at 0 and 4 weeks. Blood samples were centrifuged at 3,000 × g for 15 min at 4℃, and plasma samples were collected. Samples were stored at -80℃ for further analysis.

Levels of alkaline phosphatase (ALP), aspartate aminotransferase (AST), alanine transaminase (ALT), total cholesterol (TC), high-density lipoprotein (HDL), LDL cholesterol, triglyceride (TG), fasting plasma glucose, C-reactive protein (CRP), and testosterone were measured in plasma. ALP, AST, ALT, TC, TG, and CRP were measured enzymatically with the AVIDA 1650 instrument (Bayer), whereas HDL cholesterol levels were measured after precipitation of the other lipoproteins. LDL cholesterol levels were calculated by the Friedewald equation [19], and testosterone was measured by radioimmunoassay (Siemens).

Lipid peroxidation was measured by thiobarbituric acid-reactive substances (TBARS) using the malondialdehyde (MDA)-thiobarbituric acid assay adopted from Jentzsch *et al*. [20]. To measure antioxidant enzymes activity in plasma, superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx) activities were measured using assay kits, according to the manufacturer's instructions (Caymen Chemical, Ann Arbor, MI, USA).

Dietary assessment

Dietary intake was assessed with a 2-day food record method. Study subjects were provided with instructions to complete their food record and were asked to document their food consumption on any one weekday and any one weekend day. Subjects were asked to include food labels and recipes for mixed dishes and were encouraged to avoid any alterations to their normal diet. To ensure an adequate level of detail when describing foods and food preparation methods, the food records were carefully reviewed by a trained nutritionist immediately after completion. Dietary data were analyzed using the Can-Pro nutrient analysis software package version 3.0 (The Korean Nutrition Society, Seoul, Korea), which contains the Korean food composition table. When the food recorded could not be matched exactly with the database, the best possible match was found and used as a substitute.

Table 1. Components of the *Rubus coreanus* Miquel (RCM) supplement

Components	Amounts
Freeze-dried *Rubus C. Miquel*	30.0 g
Carboxymethyl cellulose	0.3 g
Sucrose	7.0 g
Methyl-p-Hydroxybenzoate	0.1 g
Water	150 ml

Statistical analysis

All analyses were performed with a significance level of $\alpha = 0.05$ using the SAS system (version 9.1 SAS Institute Inc, Cary, NC, USA). Continuous variables are presented as mean ± SD, and categorical variables are presented as frequencies (percentages). The paired *t*-test was performed to identify differences in the means before and after RCM supplementation.

Results

The nutrient content of freeze-dried RCM is shown in Table 2. At an energy level of 378 kcal per 100 g, the participants received 117 kcal from RCM per day. RCM contained 9.6 mg vitamin E and 1.05 g phenols, which included flavonol, flavonoids, and anthocyanins.

The general characteristics of the participants are shown in Table 3. Their average age, weight, height, and body mass index were 24.3 years, 67.5 kg, 174.9 cm, and 22.1, respectively. None

Table 2. Composition of freeze-dried *Rubus coreanus* Miquel powder

Nutrients	Amounts[1)]
Energy (kcal)	387.0
Water (g)	6.6
Lipids (g)	5.4
Proteins (g)	7.5
Carbohydrates (g)	77.1
Dietary fibers (g)	27.7
Vitamin A (mg)[2)]	1.3
Vitamin C (mg)	0.0
Vitamin E (mg)	9.6
Total phenol (g)	1.05

[1)] 100 g of freeze dried RCM

Table 3. General subject characteristics

		Subjects
Age (yrs)		24.3 ± 1.9[1)]
Weight (kg)		67.5 ± 6.1
Height (cm)		174.9 ± 5.6
BMI		22.1 ± 1.7
Previous functional food intake	Yes	13 (86.7)[2)]
	No	2 (13.3)

[1)] Mean ± SD
[2)] N (%)

Table 4. Nutrient intake of the participants

Nutrients	Recommendation level	Amounts
Energy (kcal)	2,600	2,077.6 ± 495.5[1)]
Protein (g)	55	80.1 ± 20.1
Lipids (g)		65.2 ± 15.2
Carbohydrate (g)		297.5 ± 85.3
Dietary fiber (g)	25	19.0 ± 6.6
Ca (mg)	750	565.8 ± 178.6
P (mg)	700	1,084.1 ± 242.6
Fe (mg)	10	13.5 ± 4.1
Zinc (mg)	10	9.1 ± 2.5
Vitamin A (μg RE)	750	883.7 ± 403.3
Vitamin B_1 (mg)	1.2	1.3 ± 0.4
Vitamin B_2 (mg)	1.5	1.3 ± 0.4
Vitamin B_6 (mg)	1.5	2.1 ± 0.6
Niacin (mg NE)	16	17.7 ± 5.1
Vitamin C (mg)	100	64.6 ± 25.2
Folate (μg)	400	227.8 ± 80.4
Vitamin E (mg α-TE)	12	18.8 ± 7.3
Cholesterol (mg)		363.6 ± 146.2

[1)] Mean ± SD

Table 5. Blood profiles before and after *Rubus coreanus* Miquel (RCM) supplementation

	Baseline	Post-intervention (4 weeks)
ALP (U/L)	69.47 ± 12.22	65.40 ± 11.81[1)]*
AST (U/L)	19.20 ± 4.96	19.50 ± 5.64
ALT (U/L)	17.13 ± 6.36	19.87 ± 12.74
TC (mg/dl)	184.20 ± 32.05	184.40 ± 23.41
HDL-C (mg/dl)	52.93 ± 9.65	52.20 ± 9.13
LDL-C (mg/dl)	108.47 ± 32.14	109.73 ± 23.28
TG (mg/dl)	86.00 ± 33.47	90.80 ± 39.40
Glucose (mg/dl)	87.27 ± 6.13	86.80 ± 6.30
CRP (mg/dl)	0.96 ± 2.04	0.20 ± 0.34
Testosterone (ng/ml)	6.86 ± 2.06	6.43 ± 1.41

[1)] Mean ± SD
*P< 0.05

Table 6. Lipid peroxidation and antioxidant enzyme activities in plasma before and after *Rubus coreanus* Miquel (RCM) supplementation

	Baseline	Post-intervention (4 weeks)
Lipid peroxidation (μM)	4.84 ± 0.94	4.26 ± 0.86[1)]
Plasma		
SOD (U/ml)	8.92 ± 1.66	7.49 ± 1.42
GPx (nnmol/min/ml)	108.19 ± 13.56	124.83 ± 11.89***
CAT (nnmol/min/ml)	139.75 ± 32.49	119.34 ± 41.77

[1)] Mean ± SD
***P< 0.001

of the subjects was either overweight or obese (data not shown) and 86.7% had consumed functional foods including vitamins before this study.

The nutrient intakes of the subjects are presented in Table 4. The participants consumed 2,077 kcal per day for energy, which was lower than the recommended intake for Koreans. Calcium, zinc, vitamin B_2, vitamin C, and folate intakes were lower than the recommended levels, whereas phosphorus, iron, vitamin A, vitamin B_6, and vitamin E intakes were above the recommended intake.

We examined whether RCM supplementation could modulate liver function, blood lipid profiles, fasting plasma glucose, inflammation, and testosterone level (Table 5). Every parameter was in the normal range and 4 weeks of RCM supplementation had no effect on blood lipid profiles, fasting plasma glucose, CRP, or testosterone levels, but it significantly lowered ALP levels ($P < 0.05$).

To investigate the effect of RCM supplementation on lipid peroxidation and antioxidant enzyme activities, we determined the lipid peroxidation and antioxidant enzyme activities in plasma (Table 6). RCM supplementation did not significantly lower lipid peroxidation in plasma. However, GPx activity in plasma increased significantly after the 4-week supplementation ($P < 0.001$).

Discussion

We investigated if Korean raspberry, RCM, could reduce oxidative stress by affecting antioxidant enzyme activity in healthy men. Our results showed that while RCM did not reduce lipid peroxidation, it increased plasma GPx activity.

A high fruit and vegetable intake is recognized to reduce the incidence and development of chronic diseases such as cardiovascular disease and cancer [1,2,21-23]. Several studies have shown that antioxidants in fruits and vegetable prevent chronic diseases by reducing oxidative stress, LDL oxidation, and DNA damage [24-27]. Among the antioxidants in fruits and vegetables, the health benefits of phenolic compounds have been studied, because of their high quantities and antioxidant capacity. High phenolic compound-containing foods such as fruits, teas, and wines increase plasma antioxidant capacity and reduce inflammation, cardiovascular disease, and tumorigenesis [23-28]. Recent studies have also shown that berries such as strawberries, cranberries and blueberries are good sources of phenolic compounds and dietary fiber, and that a high intake of berries increases antioxidant capacity and prevents atherosclerosis and hepatic fibrosis in human and animal studies [29-33].

RCM is prepared from a Korean raspberry that contains high concentrations of phenolic compounds. The freeze-dried RCM used as the supplement in this study contained 1.05 g total phenols per 100 g; thus, affording a daily RCM supplementation level of about 315 mg of total phenols. This was a relevant amount of phenolic compound in comparison with other high phenolic compound-containing fruits. Pears and grapes provide approximately 300 mg of total phenols per serving, and cranberries and blueberries provide about 200-400 mg [34,35]. Therefore, RCM is a good source of phenolic compounds.

RCM has traditionally been used as a Oriental medicine, and recent studies have demonstrated its antioxidant, anti-tumorigenic,

and anti-inflammatory effects in *in vitro* studies [14-17]. These effects might be related to the antioxidants present in RCM. However, as no such study has been performed with human subjects, we determined the antioxidant effect of RCM on healthy human subjects.

Our subjects ingested 65.2 g of lipids, which provided about 28% of total energy and 363.6 mg of cholesterol. These amounts were within the recommended intake range, so their blood lipid profiles were in the normal range before and after RCM supplementation. Although vitamin C intake was lower than the recommended level, vitamins A and E intake was higher than the recommended level. Other studies have reported that a high intake or supplementation with vitamins A, C, and/or E reduces lipid peroxidation and increases antioxidant enzyme activity [36,37]. Our subjects ingested high levels of antioxidants such as vitamin A and E, which means that their antioxidant capacity was already high, so the RCM supplementation may not have significantly reduce lipid peroxidation and/or increased SOD and CAT activities.

We showed that 4 weeks of RCM supplementation slightly, but not significantly, reduced lipid peroxidation from 4.84 to 4.26 μM. We tested the antioxidant effects of RCM in healthy males who did not smoke or drink alcohol, suggesting that oxidative stress levels were relatively low in our subjects. Other studies with healthy subjects also showed similar results. Six weeks of a diet with a high intake of vegetables, berries, and apples combined with linoleic acid does not reduce lipid peroxidation in healthy subjects, and moderate antioxidant supplementation does not reduce lipid and protein oxidation in healthy men [8,9]. However, strawberry supplementation significantly reduces oxidative damage and lowers TC and LDL-cholesterol levels in women with metabolic syndrome or hyperlipidemia [29-31]. These results suggest that the endogenous antioxidant defense system and antioxidant intake from the diet were adequate to prevent oxidative stress in healthy subjects, so supplementation with extra antioxidants did not reduce oxidative stress. Furthermore, the reduced level of oxidative damage may have been insufficient to produce measurable improvement.

Even though RCM supplementation did not reduce lipid peroxidation, plasma GPx activity increased. GPx is an endogenous catalytic H_2O_2 scavenger that protects against oxidative stress in cultured cells and animals [38,39]. Other studies have shown that antioxidant enzyme activities can be modulated by antioxidant or fruit supplementation [40-42]. Two months of blueberry supplementation in children with type 1 diabetes improves SOD activity in erythrocytes, and mulberry fruit supplementation increases GPx and SOD activities of red blood cells and liver in hyperlipidemic rats [41,43]. Additionally, several studies have reported that enhanced GPx activity or expression reduces the incidence of chronic diseases such as cancer, cardiovascular disease, neurodegeneration, autoimmune disease, and diabetes [44-47]. Guo et al. and Hoehn et al. showed that GPx overexpression inhibits the development of atherosclerosis and experimental stroke in animals [44,46]. However, in this study, we showed that SOD and CAT activities decreased slightly, but the difference was not significant. This result may have been caused by either the major type or concentration of phenolic compounds in RCM. Another study also showed that types or concentrations of phenolic compounds such as quercetin and rutin differentially modulate GPx, CAT, and SOD expression in HepG2 cells [48]. They showed that low-dose quercetin significantly decreases SOD but increases GPx expression levels, whereas high dose treatment significantly increases SOD but does not change CAT and GPx expression levels.

In this study, we showed that RCM supplementation may offer health benefits by enhancing antioxidant capacity in a healthy population. However, it had some limitations. First, TBARS is not a good indicator of oxidative damage because the assay relies on the reaction of thiobarbituric acid with MDA as a marker of oxidative damage to lipids. During the reaction, thiobarbituric acid may react with other oxidized products, which could modulate TBARS values. Second, self-administered dietary assessment methods tend to either under-or over-estimate diet. Even though dietary data was collected using a 2-day food record method, we could not completely prevent food intake measurement errors. Finally, we tested the antioxidant effects of RCM for 4 weeks in healthy males. Healthy males, who do not smoke and drink alcohol, have low levels of oxidative stress and high antioxidant capacity, so 4 weeks of supplementation might not have been long enough to change the antioxidant capacity and lower lipid peroxidation.

In summary, a 4-week supplementation with RCM, a Korean berry with a high phenolic content, slightly reduced lipid peroxidation and significantly increased GPx activity. Therefore, RCM is useful as a good source of fruit, which can reduce oxidative stress and provide health advantages.

References

1. Hirayama F, Lee AH, Binns CW. Dietary factors for chronic obstructive pulmonary disease: epidemiological evidence. Expert Rev Respir Med 2008;2:645-53.
2. Riccioni G, Bucciarelli T, Mancini B, Di Ilio C, Capra V, D'Orazio N. The role of the antioxidant vitamin supplementation in the prevention of cardiovascular diseases. Expert Opin Investig Drugs 2007;16:25-32.
3. Soerjomataram I, Oomen D, Lemmens V, Oenema A, Benetou V, Trichopoulou A, Coebergh JW, Barendregt J, de Vries E. Increased consumption of fruit and vegetables and future cancer incidence in selected European countries. Eur J Cancer 2010;46: 2563-80.
4. Baker H. Nutrition in the elderly: nutritional aspects of chronic diseases. Geriatrics 2007;62:21-5.
5. Lotito SB, Frei B. Consumption of flavonoid-rich foods and increased plasma antioxidant capacity in humans: cause, consequence, or epiphenomenon? Free Radic Biol Med 2006;41:1727-46.
6. Jenkins DJ, Nguyen TH, Kendall CW, Faulkner DA, Bashyam

B, Kim IJ, Ireland C, Patel D, Vidgen E, Josse AR, Sesso HD, Burton-Freeman B, Josse RG, Leiter LA, Singer W. The effect of strawberries in a cholesterol-lowering dietary portfolio. Metabolism 2008;57:1636-44.
7. Pedersen CB, Kyle J, Jenkinson AM, Gardner PT, McPhail DB, Duthie GG. Effects of blueberry and cranberry juice consumption on the plasma antioxidant capacity of healthy female volunteers. Eur J Clin Nutr 2000;54:405-8.
8. Jacob RA, Aiello GM, Stephensen CB, Blumberg JB, Milbury PE, Wallock LM, Ames BN. Moderate antioxidant supplementation has no effect on biomarkers of oxidant damage in healthy men with low fruit and vegetable intakes. J Nutr 2003;133:740-3.
9. Freese R, Alfthan G, Jauhiainen M, Basu S, Erlund I, Salminen I, Aro A, Mutanen M. High intakes of vegetables, berries, and apples combined with a high intake of linoleic or oleic acid only slightly affect markers of lipid peroxidation and lipoprotein metabolism in healthy subjects. Am J Clin Nutr 2002;76:950-60.
10. Moon GS. Constituents and Uses of Medicinal Herbs. Seoul: Ilwolbooks; 1991. p.310-1.
11. Heo J. Donguibogam. Seoul: Yeogang Publishing Co.; 1994. p.62, 296, 334, 617, 984, 1085, 2679.
12. But PPH, Guo JX, Kimura T, Sung CK, editors. International Collation of Traditional and Folk Medicine: Northeast Asia, Part II. New Jersey: World Scientific; 1997. p.68-9.
13. Cha HS, Park MS, Park KM. Physiological activities of Rubus coreanus Miquel. Korean J Food Sci Technol 2001;33:409-15.
14. Yoon I, Wee JH, Moon JH, Ahn TH, Park KH. Isolation and identification of quercetin with antioxidative activity from the fruits of Rubus coreanum Miquel. Korean J Food Sci Technol 2003;35:499-502.
15. Cho YJ, Chun SS, Kwon HJ, Kim JH, Yoon SJ, Lee KH. Comparison of physiological activities between hot-water and ethanol extracts of Bokbunja (*Rubus coreanum* F.). J Korean Soc Food Sci Nutr 2005;34:790-6.
16. Lee JW, Do JH. Determination of total phenolic compounds from the fruit and Rubus coreanum and antioxidative activity. J Korean Soc Food Sci Nutr 2000;29:943-7.
17. Jeon SK, Lee JW, Lee IS. Effect of antioxidant activity and induction of DNA damage on human gastric cancer cell by Rubus coreanus Miquel. J Life Sci 2007;17:1723-8.
18. Lee JW, Lee IJ. Effects of Rubus coreanus Miquel extracts on the activity and differentiation of MC3T3-E1 osteoblastic cell. J Life Sci 2004;14:967-74.
19. Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. Clin Chem 1972;18:499-502.
20. Jentzsch AM, Bachmann H, Fürst P, Biesalski HK. Improved analysis of malondialdehyde in human body fluids. Free Radic Biol Med 1996;20:251-6.
21. Takachi R, Inoue M, Ishihara J, Kurahashi N, Iwasaki M, Sasazuki S, Iso H, Tsubono Y, Tsugane S; JPHC Study Group. Fruit and vegetable intake and risk of total cancer and cardiovascular disease: Japan Public Health Center-Based Prospective Study. Am J Epidemiol 2008;167:59-70.
22. Loft S, Møller P, Cooke MS, Rozalski R, Olinski R. Antioxidant vitamins and cancer risk: is oxidative damage to DNA a relevant biomarker? Eur J Nutr 2008;47 Suppl 2:19-28.
23. Schroecksnadel K, Winkler C, Wirleitner B, Schennach H, Weiss G, Fuchs D. Anti-inflammatory compound resveratrol suppresses homocysteine formation in stimulated human peripheral blood mononuclear cells in vitro. Clin Chem Lab Med 2005;43:1084-8.
24. Yu YM, Chang WC, Wu CH, Chiang SY. Reduction of oxidative stress and apoptosis in hyperlipidemic rabbits by ellagic acid. J Nutr Biochem 2005;16:675-81.
25. de la Lastra CA, Villegas I. Resveratrol as an anti-inflammatory and anti-aging agent: mechanisms and clinical implications. Mol Nutr Food Res 2005;49:405-30.
26. Tobias M, Turley M, Stefanogiannis N, Vander Hoorn S, Lawes C, Mhurchu CN, Rodgers A. Vegetable and fruit intake and mortality from chronic disease in New Zealand. Aust N Z J Public Health 2006;30:26-31.
27. Chan JM, Wang F, Holly EA. Vegetable and fruit intake and pancreatic cancer in a population-based case-control study in the San Francisco bay area. Cancer Epidemiol Biomarkers Prev 2005;14:2093-7.
28. Miquel J, Bernd A, Sempere JM, Díaz-Alperi J, Ramírez A. The curcuma antioxidants: pharmacological effects and prospects for future clinical use. A review. Arch Gerontol Geriatr 2002; 34:37-46.
29. Basu A, Wilkinson M, Penugonda K, Simmons B, Betts NM, Lyons TJ. Freeze-dried strawberry powder improves lipid profile and lipid peroxidation in women with metabolic syndrome: baseline and post intervention effects. Nutr J 2009;8:43.
30. Basu A, Fu DX, Wilkinson M, Simmons B, Wu M, Betts NM, Du M, Lyons TJ. Strawberries decrease atherosclerotic markers in subjects with metabolic syndrome. Nutr Res 2010;30:462-9.
31. Henning SM, Seeram NP, Zhang Y, Li L, Gao K, Lee RP, Wang DC, Zerlin A, Karp H, Thames G, Kotlerman J, Li Z, Heber D. Strawberry consumption is associated with increased antioxidant capacity in serum. J Med Food 2010;13:116-22.
32. Wu X, Kang J, Xie C, Burris R, Ferguson ME, Badger TM, Nagarajan S. Dietary blueberries attenuate atherosclerosis in apolipoprotein E-deficient mice by upregulating antioxidant enzyme expression. J Nutr 2010;140:1628-32.
33. Wang YP, Cheng ML, Zhang BF, Mu M, Wu J. Effects of blueberry on hepatic fibrosis and transcription factor Nrf2 in rats. World J Gastroenterol 2010;16:2657-63.
34. Vinson JA, Su X, Zubik L, Bose P. Phenol antioxidant quantity and quality in foods: fruits. J Agric Food Chem 2001;49:5315-21.
35. Lotito SB, Frei B. Relevance of apple polyphenols as antioxidants in human plasma: contrasting in vitro and in vivo effects. Free Radic Biol Med 2004;36:201-11.
36. Kanter M, Coskun O, Armutcu F, Uz YH, Kizilay G. Protective effects of vitamin C, alone or in combination with vitamin A, on endotoxin-induced oxidative renal tissue damage in rats. Tohoku J Exp Med 2005;206:155-62.
37. Oztürk-Urek R, Bozkaya LA, Tarhan L. The effects of some antioxidant vitamin- and trace element-supplemented diets on activities of SOD, CAT, GSH-Px and LPO levels in chicken tissues. Cell Biochem Funct 2001;19:125-32.
38. Mirault ME, Tremblay A, Furling D, Trepanier G, Dugre F, Puymirat J, Pothier F. Transgenic glutathione peroxidase mouse models for neuroprotection studies. Ann N Y Acad Sci 1994;738: 104-15.
39. Comhair SA, Erzurum SC. The regulation and role of extracellular glutathione peroxidase. Antioxid Redox Signal 2005;7:72-9.
40. Duthie SJ, Jenkinson AM, Crozier A, Mullen W, Pirie L, Kyle J, Yap LS, Christen P, Duthie GG. The effects of cranberry juice consumption on antioxidant status and biomarkers relating to

heart disease and cancer in healthy human volunteers. Eur J Nutr 2006;45:113-22.
41. Nemes-Nagy E, Szocs-Molnár T, Dunca I, Balogh-Sămărghiţan V, Hobai S, Morar R, Pusta DL, Crăciun EC. Effect of a dietary supplement containing blueberry and sea buckthorn concentrate on antioxidant capacity in type 1 diabetic children. Acta Physiol Hung 2008;95:383-93.
42. Lee SJ, Choi SK, Seo JS. Grape skin improves antioxidant capacity in rats fed a high fat diet. Nutr Res Pract 2009;3:279-85.
43. Yang X, Yang L, Zheng H. Hypolipidemic and antioxidant effects of mulberry (Morus alba L.) fruit in hyperlipidaemia rats. Food Chem Toxicol 2010;48:2374-9.
44. Guo Z, Ran Q, Roberts LJ 2nd, Zhou L, Richardson A, Sharan C, Wu D, Yang H. Suppression of atherogenesis by overexpression of glutathione peroxidase-4 in apolipoprotein E-deficient mice. Free Radic Biol Med 2008;44:343-52.
45. Hoehn B, Yenari MA, Sapolsky RM, Steinberg GK. Glutathione peroxidase overexpression inhibits cytochrome C release and proapoptotic mediators to protect neurons from experimental stroke. Stroke 2003;34:2489-94.
46. Weisbrot-Lefkowitz M, Reuhl K, Perry B, Chan PH, Inouye M, Mirochnitchenko O. Overexpression of human glutathione peroxidase protects transgenic mice against focal cerebral ischemia/reperfusion damage. Brain Res Mol Brain Res 1998;53:333-8.
47. Lei XG, Cheng WH, McClung JP. Metabolic regulation and function of glutathione peroxidase-1. Annu Rev Nutr 2007;27: 41-61.
48. Alía M, Mateos R, Ramos S, Lecumberri E, Bravo L, Goya L. Influence of quercetin and rutin on growth and antioxidant defense system of a human hepatoma cell line (HepG2). Eur J Nutr 2006;45:19-28.