JOURNAL OF CANCER PREVENTION
VOL. 20, NO. 3, SEPTEMBER, 2015

http://dx.doi.org/10.15430/JCP.2015.20.3.202
pISSN 2288-3649 · eISSN 2288-3657

Antioxidative Activity of Onion Peel Extract in Obese Women: A Randomized, Double-blind, Placebo Controlled Study

ORIGINAL ARTICLE

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Background: Quercetin, found abundantly in onion peel, has been known to have anticholesterol, antithrombotic and insulin-sensitizing properties. Here, we investigated the effect of quercetin-rich onion peel extract (OPE) on reactive oxygen species (ROS) production and antioxidative defense in obese woman.
Methods: This study was randomized, double-blind, placebo controlled study. Thirty-seven healthy obese participants were randomly assigned that eighteen subjects received red soft capsuled OPE (100 mg/d, 50 mg bis in die), while the other nineteen subjects received same capsuled placebo for 12 weeks. ROS production and superoxide dismutase (SOD) activity in plasma were determined by using ROS and SOD assay kits, respectively.
Results: Baseline characteristics of anthropometric indicators and blood metabolic profiles were not significantly different between the two groups. Compared with baseline values, OPE consumption significantly reduced waist and hip circumference. Plasma ROS level and SOD activity were decreased in both placebo and OPE groups compared with baseline values. However, plasma ROS level in OPE group was significantly lower than in placebo group while plasma SOD activity in OPE group was significantly higher than in placebo group after 12 weeks of consumption.
Conclusions: These findings indicate that OPE consumption may exert antioxidative effect by preventing the decrease of SOD activity as well as the production of ROS in obese women.
(J Cancer Prev 2015;20:202-207)

Key Words: Onion peel extract, Quercetin, Reactive oxygen species, Superoxide dismutase

INTRODUCTION

There is considerable evidence linking continued oxidative stress to the development of chronic inflammation, which in turn could mediate most chronic diseases including cancer, diabetes, aging, and vascular disorders.[1-3] Oxidative stress is characterized as the disruption of intracellular balance between generation of free radicals and reactive metabolites (often called as oxidants or reactive oxygen species [ROS]), and their destruction by protective systems and mechanisms, referred to as antioxidants.[3] Most ROS, generated in cells via the mitochondrial respiration, are products of a normal cellular oxidative metabolism. Under physiologic conditions, cells generate ROS such as superoxide anion radical (O_2^-), hydroxyl radical (OH・), hydrogen peroxide (H_2O_2), and organic peroxides as normal products of the biological reduction of molecular oxygen.[4] However, under a sustained oxidative stress, ROS are generated over a long time and thus affect cellular viability, metabolism, and function which may lead to the development of chronic diseases including vascular disorders neurodegenerative diseases, diabetes mellitus, and tumor diseases.[2,5-8] Even physiological processes such as aging are also defined as an increase in oxidative stress as a results of progressive decrease in the ROS elimination.[9] To fight excessive production of these harmful pro-oxidants, the organism has built protective systems such as enzymatic antioxidants (e.g., superoxide dismutase [SOD], glutathione peroxidase [GPX], glutathione

Received August 3, 2015, **Revised** August 24, 2015, **Accepted** August 25, 2015

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reductase, and catalase) and non-enzymatic antioxidants (e.g., glutathione [GSH], vitamins C, and D).[10] Disturbances in the balance between the generation of ROS and antioxidant defenses of cells lead to the accumulation of molecular damage in proteins, lipids, and DNA, with potential impact on the whole organism.[3] To enhance antioxidant system capable of reducing oxidative stress to eventually prevent chronic diseases associated with continued oxidative stress, the application of food-derived antioxidants has recently become a focus of interest.

The polyphenol quercetin, found abundantly in onion peel, is one of the major plant-derived flavonoid. It has been known to have antiobesity, antidiabetes, and antihypertensive effects in animal models and human studies.[11-16] Quercetin could also sensitize resistant cancer cells to chemotherapy and synergize the effect of drugs in nonresistant cancer cell.[17] In addition, previous studies have demonstrated that quercetin-rich onion peel extract (OPE) treatment has antiplatelet, antiadipogenic, and anti-inflammatory property in vitro as well as in animal models.[18-22] Thus far, there is no study to examine the effect of treatment with OPE on the antioxidant system in obese human. Therefore, in the present study, we evaluated the effect of quercetin-rich OPE supplementation for 12 weeks on ROS production and antioxidative defense in obese woman.

MATERIALS AND METHODS

1. Subjects

This study was randomized, double-blind, placebo controlled study. Thirty-seven healthy obese participants were recruited. The study was approved by the institutional review board of Kyung Hee Medical Center (KMC IRB 1304-03-C1). Subjects who had hypertension and diabetes were excluded from this study. And, subjects with who were taking dietary restriction drugs or were participating diet programs were excluded from this study.

2. Onion peel extract preparation

OPE were prepared from Newfood Co., Changnyung, Korea. OPE were washed, extracted with 60% ethanol, filtered, concentrated, and processed to give a powder. Analyses of total phenol, total flavonoid, and quercetin contents yielded the following values: 681.7, 372.0, and 286.0 mg/g, respectively.

3. Study protocol

Thirty-seven healthy obese participants were randomly assigned using a computerized random allocation sequence that eighteen subjects received red soft capsuled OPE (100 mg/d, 50 mg bis in die), while the other nineteen subjects received same capsuled placebo for 12 weeks. Plasma was obtained by centrifugation of blood at 1,500 $\times g$ for 15 minutes which was stored at $-80^{\circ}C$ until analyzed.

4. Anthropometric and biochemical analysis

Anthropometric measurements were taken at baseline and at 12 weeks. Body mass index (BMI) was calculated as weight in kilogram divided by height in meters squared; waist and hip circumference were also measured. Fat mass were measured by bioimpedance analysis (Inbody 3.0; Biospace, Seoul, Korea). Systolic blood pressure and diastolic blood pressure (DBP) was measured from the left arm in seated patients with an automatic blood pressure monitor (TM-2654; A&D, Tokyo, Japan) after a 20 minutes rest. Two measurements were taken at least 5 minutes apart, and the mean was used for analysis. Plasma triglyceride, total cholesterol, low-density lipoprotein cholesterol, and high-density lipoprotein-cholesterol were measured with commercially available kits (Bayers, Tarrytown, NY, USA) using enzymatic methods.

5. Determination of reactive oxygen species concentration

Plasma ROS levels was determined using OxiSelect Intracellular ROS Assay Kit (Cell Biolabs Inc., San Diego, CA, USA), according to the manufacturer's instructions. Briefly, ROS species react with 2′,7′-dichlorodihydrofluorescein (DCFH), which is rapidly oxidized to the fluorescent DCFH. Its fluorescence intensity is proportional to the total ROS levels within the sample and was quantified by a spectrophotometer (Spectramax M2; Molecular Devices, Sunnyvale, CA, USA) at 480 nm/530 nm with 530 nm cutoff.

6. Determination of superoxide dismutase activity

Plasma SOD activity was determined by a competitive colorimetric inhibition assay using SOD activity kit (ENZO life Sciences, Plymouth Meeting, PA, USA), according to the manufacturer's instructions. Briefly, samples or standards (25 μL) were incubated with 150 μL reaction mixture containing WST-1 and Xanthine oxidase and then xanthine solution was added. Formazan formation was measured at 450 nm using a 96-well plate reader (Spectramax M2; Molecular Devices). SOD concentration, expressed in units per milligram of protein, was determined using the SOD standard curve.

7. Statistical analysis

Statistical analysis was performed with the SAS ver. 9.1 software package (SAS Institute Inc., Cary, NC, USA). Data were expressed as means ± SD. Significantly different before and after placebo or OPE intakes by paired *t*-test. The difference between the OPE and placebo groups was analyzed using *t*-test. Differences were considered significant at $P < 0.05$.

RESULTS

1. Effects of onion peel extract on anthropometric measurements

Baseline characteristics of anthropometric indicators were not significantly different between the two groups. On assessing body weight, BMI, fat mass, and blood pressure after 12 weeks, no significant difference was found between the placebo and OPE treatment. However, OPE consumption significantly reduced waist and hip circumferences, compared with baseline values (Table 1).

Table 1. Changes in anthropometric measurement

Variable	Placebo (n = 19)			Onion peel extract (n = 18)		
	Baseline	12 weeks	Change	Baseline	12 weeks	Change
Age (yr)	45.4 ± 9.5	–	–	44.6 ± 7.6	–	–
Height (cm)	159.0 ± 6.3	–	–	159.2 ± 4.1	–	–
Weight (kg)	67.2 ± 6.8	67.2 ± 6.6	0.02 ± 3.86	65.9 ± 9.2	65.4 ± 8.9	−0.68 ± 1.76
BMI (kg/m^2)	26.6 ± 2.5	26.6 ± 2.4	0.02 ± 3.86	26.0 ± 3.8	25.8 ± 3.6	−0.68 ± 1.76
Waist (cm)	88.9 ± 7.1	88.5 ± 6.9	−0.46 ± 2.51	90.5 ± 8.3	88.3 ± 7.8[a]	−2.33 ± 2.77
Hip (cm)	99.9 ± 5.7	99.1 ± 5.3	−0.58 ± 1.67	99.9 ± 5.6	98.5 ± 6.1[a]	−1.37 ± 2.14
Fat mass (kg)	23.6 ± 4.53	23.4 ± 4.05	0.24 ± 10.57	23.7 ± 6.30	23.4 ± 5.9	−1.13 ± 5.52
SBP (mmHg)	117.3 ± 14.7	117.7 ± 13.3	0.83 ± 8.47	110.1 ± 9.3	110.1 ± 9.4	0.39 ± 8.80
DBP (mmHg)	74.3 ± 9.4	75.5 ± 7.8	2.20 ± 9.04	69.6 ± 8.2	68.1 ± 6.5	−1.04 ± 12.93

Values are presented as mean ± SD. BMI, body mass index; Waist, waist circumference; Hip, hip circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure. [a]*P*-value < 0.05, significantly different before and after placebo or onion peel extract intakes by paired *t*-test.

Table 2. Changes in blood metabolic profiles

Variable	Placebo (n = 19)			Onion peel extract (n = 18)		
	Baseline	12 weeks	Change	Baseline	12 weeks	Change
Triglyceride (mg/dL)	108.6 ± 44.4	116.9 ± 43.0	14.22 ± 36.47	98.8 ± 35.5	95.0 ± 28.8	2.13 ± 28.92
TC (mg/dL)	193.6 ± 37.4	187.9 ± 35.6	−1.56 ± 14.10	183.6 ± 34.9	193.1 ± 28.7	8.25 ± 26.11
LDL-C (mg/dL)	122.2 ± 33.9	118.8 ± 31.8	0.38 ± 21.87	118.3 ± 30.6	126.8 ± 29.3	12.63 ± 41.72
HDL-C (mg/dL)	55.2 ± 9.2	53.5 ± 8.6	−2.17 ± 11.94	51.7 ± 9.9	53.6 ± 9.7	4.96 ± 16.84
Leptin (ng/mL)	15.2 ± 7.8	12.8 ± 6.1	−12.55 ± 30.86	16.9 ± 11.6	13.3 ± 7.3	−7.31 ± 50.95

Values are presented as mean ± SD. TC, total cholesterol; LDL-C, low-density lipoprotein-cholesterol; HDL-C, high-density lipoprotein-cholesterol.

Table 3. Changes in plasma ROS levels and SOD activity

	Placebo (n = 19)			Onion peel extract (n = 18)		
	Baseline	12 weeks	Change	Baseline	12 weeks	Change
ROS (nM)	147.9 ± 32.7	137.8 ± 61.6[a]	−1.55 ± 52.66	158.8 ± 22.8	123.5 ± 45.4[a]	−21.54 ± 31.73[b]
SOD (U/mg protein)	1.96 ± 0.26	1.45 ± 0.38[a]	−23.77 ± 23.20	1.95 ± 0.20	1.60 ± 0.25[a]	−17.68 ± 9.42[b]

Values are presented as mean ± SD. ROS, reactive oxygen species; SOD, superoxide dismutase. [a]$P < 0.05$, significantly different before and after placebo or onion peel extract intakes by paired *t*-test. [b]$P < 0.05$, significantly different in placebo and onion peel extract by *t*-test.

2. Effects of onion peel extract on blood metabolic profiles parameters

As shown in Table 2, characteristics of blood metabolic profiles before and after the 12-week treatment were not significantly different between the two groups.

3. Effects of onion peel extract on reactive oxygen species level and superoxide dismutase activity

Plasma ROS level and SOD activity changed significantly after 12 weeks of treatment with placebo or OPE (Table 3). However, plasma ROS level in OPE-treated group was significantly lower than in placebo group while plasma SOD activity in OPE-treated group was significantly higher than in placebo group.

DISCUSSION

The aim of the present randomized, double-blind, placebo controlled study was to investigate the effect of a 12-week supplementation with quercetin-rich OPE on ROS production and antioxidative defense in obese women. Our major finding was that OPE supplementation significantly prevented the decrease of SOD activity and the production of ROS.

Numerous studies suggest the suppressive effects of quercetin and quercetin-rich OPE against obesity in animal models and cell lines. In mice fed a Western diet or high-fat diet, quercetin reduced liver fat accumulation by regulating the expression of lipid metabolism genes.[11,13] In obese Zucker rats, Rivera et al.[12] demonstrated that quercetin also had anti-inflammatory effects in the visceral adipose tissue and reduced body weight gain. In 3T3-L1 cells, quercetin and quercetin-rich OPE were reported to attenuate adipogenesis.[19,22,23] Recently, Yang and Kim[24] demonstrated that the obesity index (% fat, BMI, waist circumstance) were significantly decreased by OPE intake for 12 weeks in obese university women. However, another study reported that no changes were observed in body weight and BMI in healthy young women with OPE supplementation for 2 weeks.[25] In the current study, we also found that OPE supplementation significantly reduced waist and hip circumferences, compared with baseline values. However, the changes observed in body weight and BMI were not statistically significant after 12 weeks of OPE supplementation. Since abdominal obesity has been identified as an independent risk factor for metabolic diseases and waist circumference as well as waist-to-hip ratio has been shown to be better markers of metabolic risk than BMI among many anthropometric measures for central body fat assessment,[26-28] our results are in line with the previous studies showing antiobesity effects of OPE.

Recently, Egert et al.[16] have shown that quercetin for 6 weeks in people with metabolic syndrome compared with the placebo group significantly decreased the systolic and DBPs. In addition, Edwards et al.[29] have demonstrated that quercetin supplementation for 4 weeks in pre-hypertensives and stage 1 hypertensive individuals significantly reduced systolic and DBPs only in stage 1 hypertensive subjects while no significant differences were found between two groups. In our study, OPE supplementation did not attenuate the blood pressure in obese women with normal blood pressure. This finding is consistent with the study conducted by Conquer et al.[30] which examined the effect of quercetin supplementation on blood pressure in healthy subjects and reported that quercetin for 4 weeks could not have a significant effect on systolic and DBP. It seems likely that the blood pressure-lowering effect of quercetin is related to the degree of hypertension. Indeed, Lee et al.[31] reported that daily quercetin-rich supplementation from OPE for 10 weeks significantly decreased both systolic and DBP in pre-hypertentive male smokers.

In many animal studies, quercetin is known to have antioxidant properties. Pre-treatment of quercetin may protect against ethanol-induced oxidative stress in mouse liver by directly quenching lipid peroxides and indirectly by enhancing the production of the endogenous antioxidant GSH.[32] Galisteo et al.[33] investigated the potential of chronic administration of dietary flavonoid quercetin to prevent hypertension as well as oxidative stress induced by deoxycorticosterone acetate-salt in rats and found that antihypertensive effect of quercetin accompanied by normalization of plasma thiobarbituric acid reactive substances (TBARS) values, improvement of the antioxidant defense system in heart and liver, restoring total GSH levels in both organs and altered liver glutathione S-transferase and GPX activities. However, human studies to investigate the antioxidative effect of quercetin have shown contradictory results which may associated with difference of physiology in humans and animals as well as levels of oxidative status.[29,34] In addition, there are only few studies that examined the effect of OPE supplementation on ROS production and antioxidative defense in animals and humans. Park et al.[35] demonstrated that dietary onion flesh or onion peel supplementation was beneficial for lowering lipid peroxides levels such as plasma total antioxidant status, liver TBARS, and brain 8-isoprrostance levels in aged rats. Previously, Kim et al.[25] reported that OPE supplementation for 2 weeks significantly modified the lipid profile and atherogenic index while no changes observed in activities of antioxidant enzymes or levels of

lipid peroxidation markers in healthy young women. In the current study, we observed that plasma ROS level and SOD activity changed significantly after 12 weeks of treatment with placebo or OPE; however, plasma ROS level in OPE-treated group was significantly lower than in placebo group while plasma SOD activity in OPE-treated group was significantly higher than in placebo group. These results can be attributed to the difference of subjects (healthy normal-weight women vs. obese women) and study design (2 weeks vs. 12 weeks of supplementation with OPE).

In conclusion, our findings demonstrate that OPE supplementation may exert antioxidative effect by preventing the decrease of SOD activity and the production of ROS in obese women. To the best of our knowledge, there is no study to investigate the antioxidative effect of quercetin-rich OPE in obese women. Since free radicals and their reactive metabolites including ROS have emerged as important regulators of many physiological and pathological processes, OPE consumption may be beneficial for obese individuals as a means of reducing oxidative stress to eventually prevent chronic diseases associated with continued oxidative stress.

ACKNOWLEDGMENTS

This research is financially supported by Changwon National University in 2015-2016.

CONFLICTS OF INTEREST

No potential conflicts of interest were disclosed.

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