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Original Article

The Effect of Onion Peel Extract on Inflammatory Mediators in Korean Overweight and Obese Women

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Conflict of Interest
The authors have no potential conflicts of interest to disclose.

ABSTRACT

Quercetin, found abundantly in onion peel, has been known to have antioxidant and anti-obesity effects and improves endothelial function. The purpose of this study was to evaluate the effects of a quercetin-rich onion peel extract (OPE) on the inflammatory mediators in overweight and obese women. This study was a randomized double-blind, placebo-controlled study. Thirty-seven healthy overweight and obese women were randomly assigned to two groups, and one group was given a soft capsuled OPE (100 mg quercetin/day, n = 18) and the other group a same capsuled placebo (n = 19) for 12 weeks. Fat mass was measured by bioimpendance method at baseline and after 12 weeks of intervention. The levels of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were measured with colorimetric assay kits. The concentrations of leptin, adiponectin, visfatin, tumor necrosis factor (TNF)-α and interleukin (IL)-4 in plasma were determined by using enzyme-linked immunosorbent assay kits. Baseline characteristics of anthropometric indicators and blood metabolic profiles were not significantly different between placebo and OPE groups. Compared with baseline value, both placebo and OPE supplementation significantly decreased the percent of body fat mass and induced plasma adiponectin levels while ALT and AST activities as well as leptin, visfatin, TNF-α, and IL-4 levels in plasma were not significantly different between two groups after 12 weeks of the supplementation. These findings suggest that 12-week supplementation of OPE do not affect modulators of systemic inflammation in overweight and obese women.

Keywords: Onion peel extract; Quercetin; Obesity; Inflammation; Adiponectin

INTRODUCTION

The prevalence of overweight and obesity is increasing at an alarming rate worldwide. In the analyses for the Global Burden of Disease Study, Ng et al. [1] reported that about 37% of men and 27% of women were obese (body mass index [BMI] ≥ 25 kg/m^2) in South Korea. Obesity and its associated metabolic alterations are linked with a chronic low-grade systemic inflammatory response, which is characterized by abnormal production of pro-inflammatory cytokines and activation of inflammatory signaling pathways [2]. Extensively reviewed evidences demonstrate that adipose tissue plays an important role in inflammation and thus acts as a major contributor to the elevation of inflammatory activity [3]. Indeed, various

Author Contributions

Kyung-Ah Kim was responsible for experimental anaysis and writing of manyscript and Jung-Eun Yim was responsible for study design, experimental anaysis, and writing of manuscript.

secreted products from adipocytes/adipose tissue, so called adipokines or adipocytokines, have been characterized. Adipokines, adiponectin, leptin, resistin, and visfatin are considered as an important link between obesity and related inflammatory diseases [4]. Furthermore, the infiltration of macrophages in adipose tissue and then altered production of inflammatory cytokines such as tumor necrosis factor (TNF)-α and interleukin (IL)-4 may contribute to the mechanisms underlying the development of inflammation [5,6]. Therefore, the application of natural resources such as vegetables has recently become a focus of interest as potential source of anti-inflammatory substances to prevent obesity and its associated metabolic diseases.

Quercetin, found abundantly in onion peel, is one of the major plant-derived flavonoids. It has been known to have anti-diabetes, anti-obesity, and anti-hypertensive effects in animal and human studies [7-10]. Recently, we reported that 12-week supplementary intake of quercetin-rich onion peel extract (OPE) significantly decreased body weight and percentage of body fat in overweight and obese adults [11]. We also have demonstrated that quercetin-rich OPE consumption for 12 weeks may exert antioxidative activity by preventing the reduction of superoxide dismutase (SOD) activity as well as the production of reactive oxygen species (ROS) in obese women [12]. In addition, several recent studies have demonstrated that OPE has anti-inflammatory property in vitro as well as in animal models [13,14]. However, little has been known about the effect of OPE on the inflammatory mediators in obese human. Therefore, the aim of this study was for the first time to examine the effect of quercetin-rich OPE supplementation on the pro- and anti-inflammatory mediators in overweight and obese women.

MATERIALS AND METHODS

Subjects

This study was a 12-week, randomized, double-blind, placebo-controlled study. Thirty-seven overweight and obese women were recruited (BMIs > 23 kg/m^2). The study was approved and conducted by the institutional review board of Kyung Hee Medical Center (KMC IRB 1304-03-C1), and all subjects agreed to participate in this study and signed written informed consents forms. Subjects who had psychological disease, hypertension, diabetes mellitus, infectious diseases, and medical or surgical illness within 3 months of enrollment were excluded from the study.

Study design

We randomly assigned using a computerized random allocation sequence of thirty-seven subjects of whom nineteen were assigned to a placebo and another eighteen were assigned to an OPE. The OPE was acquired from Changnyeong between August and September 2012, and passed through an OPE powder manufacturing process [15]. The OPE group was received 100 mg of quercetin [15] daily for 12 weeks, while placebo group was treated with identically-packaged soft capsules containing lactose mixture [16].

Anthropometric analysis

Anthropometric measurements were measured at baseline and at 12th week of intervention. Body weight and height were measured twice by a single trained registered dietitian. BMI was calculated as weight in kg divided by height in meters squared. Fat free mass (FFM), body fat mass (BFM), and percent of body fat mass (PBFM) were measured by bioimpedance analysis (Inbody 3.0; Biospace, Seoul, Korea).

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Biochemical analysis

The blood samples of subjects were taken baseline and at 12 weeks of intervention, and were collected after a 12-hour overnight fasting. The samples were centrifuged and plasma were frozen and stored at −60°C. Plasma levels of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were measured with colorimetric method using enzymatic analysis kits (Asan Phamaceuticals Co., Ltd., Hwasung, Korea). Plasma levels of adiponectin and leptin were measured by an enzyme-linked immunosorbent assay (ELISA) using Alpco kits (ALPCO Diagnostics; Salem, NH, USA). Visfatin was analyzed by a sandwich ELISA using kits from LifeSpan BioSciences, Inc. (Seattle, WA, USA). TNF-α and IL-4 levels were determined using ELISA kits from Enzo Life Sciences, Inc. (Farmingdale, NY, USA).

Statistical analysis

The data in this study were statistically analyzed with the Statistical Analysis System software package (SAS 9.1; SAS Institute Inc., Cary, NC, USA). Data were expressed as means and standard deviation values. The anthropometric data and biochemical data from placebo and OPE-treated groups before and after the intervention were analyzed by a paired t-test. The difference between the placebo and OPE-treated groups was analyzed by a t-test. All statistical results were defined as a p value less than 0.05.

RESULTS

Effects of OPE on anthropometric measurements

Baseline characteristics of anthropometric indicators were not significantly different between the two groups. On assessing body weight, BMI, FFM, and BFM after 12 weeks of supplementation, no significant difference was found between the placebo and OPE-treated groups. Compared with baseline values, both placebo and OPE significantly reduced PBFM while no significant inter-group difference was found (**Table 1**).

Effects of OPE on plasma metabolic parameters

The activities of ALT and AST before and after the 12-week treatment were not significantly different between the two groups (**Table 2**).

Plasma adipokines, adiponectin levels were increased in placebo and OPE-treated groups compared with baseline values. However, no significant differences were found between the two groups (**Table 3**). Compared with baseline values, the levels of IL-4 and TNF-α were

Table 1. Anthropometric measurement of subjects during 12 weeks of intervention

Variables	Placebo (n = 19)			OPE (n = 18)		
	Baseline	12 wk	Change, %	Baseline	12 wk	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 ± 3.90	65.9 ± 9.2	65.4 ± 8.9	−0.68 ± 1.80
BMI, kg/m^2	26.6 ± 2.5	26.6 ± 2.4	0.02 ± 3.90	26.0 ± 3.8	25.8 ± 3.6	−0.68 ± 1.80
FFM, kg	43.7 ± 3.9	23.8 ± 4.2	0.30 ± 3.10	42.1 ± 4.4	22.0 ± 4.5	−0.30 ± 2.30
BFM, kg	23.6 ± 4.5	23.4 ± 4.1	0.20 ± 5.20	23.7 ± 6.3	23.4 ± 5.9	−1.10 ± 5.50
PBFM, %	34.9 ± 4.1	34.7 ± 3.8*	−0.30 ± 5.20	39.0 ± 15.3	35.4 ± 4.6*	−4.00 ± 14.80

Values are mean ± standard deviation (SD).

OPE, onion peel extract; BMI, body mass index; FFM, fat free mass; BFM, body fat mass; PBFM, percent of body fat mass.

*p value < 0.05, significant difference before and after placebo or OPE intakes by paired t-test.

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Table 2. Changes in AST and ALT activities

Variables	Placebo (n = 19)			OPE (n = 18)		
	Baseline	12 wk	Change, %	Baseline	12 wk	Change, %
AST, IU/L	21.9 ± 5.5	18.4 ± 3.5	−13.0 ± 18.0	25.3 ± 12.4	23.4 ± 16.5	−3.3 ± 35.0
ALT, IU/L	16.1 ± 5.0	14.2 ± 4.9	−7.4 ± 29.6	22.9 ± 16.3	22.0 ± 22.4	0.0 ± 39.5

Values are mean ± standard deviation (SD).

OPE, onion peel extract; AST, aspartate aminotransferase; ALT, alanine aminotransferase.

*p value < 0.05, significant difference before and after placebo or OPE intakes by paired t-test.

Table 3. Changes in plasma adipokines

Variables	Placebo (n = 19)			OPE (n = 18)		
	Baseline	12 wk	Change, %	Baseline	12 wk	Change, %
Leptin, ng/mL	15.2 ± 7.8	12.8 ± 6.1	−12.6 ± 30.9	16.9 ± 11.6	13.3 ± 7.3	−7.3 ± 51.0
Adiponectin, μg/mL	3.8 ± 1.5	6.4 ± 1.8*	94.1 ± 47.0	3.6 ± 2.0	6.9 ± 2.3*	118.5 ± 114.2
Visfatin, ng/mL	0.9 ± 0.6	0.6 ± 0.4	−9.3 ± 73.5	1.0 ± 0.7	1.0 ± 1.1	−22.0 ± 66.0
TNF-α, pg/mL	201.3 ± 18.2	203.9 ± 22.4	2.6 ± 23.2	201.6 ± 22.7	207.3 ± 22.9	5.6 ± 27.2
IL-4, pg/mL	11.7 ± 5.1	15.5 ± 6.8	3.7 ± 8.7	12.0 ± 7.2	18.4 ± 10.5	6.4 ± 14.4

Values are mean ± standard deviation (SD).

OPE, onion peel extract; TNF, tumor necrosis factor; IL, interleukin.

*p value < 0.05, significant difference before and after placebo or OPE intakes by paired t-test.

increased while those of leptin and visfatin were decreased in placebo and OPE-treated groups, although these results did not reach statistical significance in intra-group as well as inter-group comparison.

DISCUSSION

The aim of this randomized, double-blind, placebo-controlled study was to examine for the first time effects of a 12-week supplementation with quercetin-rich OPE on the inflammatory mediators in overweight and obese women. In the present study, we found that OPE supplementation significantly decreased the PBFM and induced plasma adiponectin levels compared with baseline values, while no significant difference was found between placebo and OPE-treated groups. In addition, leptin, visfatin, TNF-α, and IL-4 levels in plasma were not significantly different between the two groups before and after 12 weeks of supplementation.

Several recent studies suggest the suppressive effects of quercetin and quercetin-rich OPE against obesity in cell lines and animal models. In 3T3-L1 cells, quercetin and quercetin-rich OPE attenuated adipogenesis [17,18] and decreased liver fat accumulation in mice fed a Western diet or high-fat diet (HFD) [7,9]. Recently, Yang and Kim [19] demonstrated that the obesity index (% fat, BMI, waist circumstance) were significantly decreased by OPE intake for 12 weeks in obese university women. Previously, we reported that OPE supplementation significantly reduced the weight and percentage of body fat in overweight and obese adults [11]. We also reported that OPE supplementation significantly reduced waist and hip circumferences compared with baseline values while the changes observed in body weight and BMI were not statistically significant after 12 weeks of supplementation [12]. However, another study reported that no significant difference was observed in body weight and BMI in healthy young women with OPE supplementation for 2 weeks [15]. In the present study, we observed that OPE supplementation significantly decreased the PBFM but without a significant effect in inter-group comparison. Smaller pool of subjects in this study was a

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probable reason of different results in body weight and PBFM compared with other studies which found anti-obesity effect of OPE.

It is widely accepted that obesity is associated with low-grade chronic inflammatory responses, characterized by abnormal cytokine production and the activation of pro-inflammatory signaling pathways [2]. Numerous studies suggest that adipocytes and diverse types of infiltrated immune cells such as macrophages and T lymphocytes in adipose tissue play a vital role in inflammation by releasing bioactive inflammatory mediators so called adipokines [4]. These include highly active cytokines, mainly produced by adipocytes like adiponectin, leptin, resistin, and visfatin, as well as some more classical cytokines produced by infiltrated inflammatory cells like TNF-α, IL-6, and IL-4.

Adiponectin is the most abundant adipokine and serum levels of adiponectin are markedly decreased in individuals with visceral obesity and adiponectin levels correlate inversely with insulin resistance [20]. Adiponectin has been demonstrated to have anti-inflammatory effects by inhibiting NF-κB activation in endothelial cells and inducing the production of the anti-inflammatory cytokines in human leukocytes [21,22]. In animal models of liver inflammation, adiponectin exerts anti-inflammatory effects by suppressing the expression of TNF-α and attenuating liver fibrosis [23,24]. Recently, Kim et al. [14] reported that quercetin-rich OPE supplementation increased the adiponectin production at a transcription level in the high fat diet-induced obese animal model, suggesting that quercetin-rich OPE has modulatory effect on the inflammatory processes in obesity. Furthermore, quercetin increased levels of secreted adiponectin in TNF-α-treated 3T3-L1 adipocytes [25] as well as in obese Zucker rats [8] and diet-induced obese mice [26]. In the present study, adiponectin levels in placebo and OPE-treated groups were increased compared with baseline values. However, no significant differences were found between the two groups. This finding is consistent with the study conducted by Brüll et al. [27] which reported that 6-week treatment with quercetin did not significantly affect serum concentrations of adiponectin and leptin, compared to placebo in obese humans.

Similar to adiponectin, leptin is produced by adipocytes. It is involved mainly in the regulation of food intake and serum levels of leptin are proportional to adipose tissue mass in both animals and humans [28,29]. In contrast to adiponectin, leptin is generally considered to be a pro-inflammatory cytokine. The concentration of leptin is increased in inflammatory conditions in animal model [30,31] and in rheumatoid arthritis patients [32]. In animal model, quercetin reduced both plasma leptin and expression of leptin in adipose tissue from mice fed the Western diet for 18 weeks [26]. However, we observed that neither placebo nor OPE supplementation significantly changed the concentration of leptin. Wein et al. [33] also reported that quercetin feeding for 4 weeks did not affect plasma leptin levels in HFD fed rats.

Visfatin, originally identified as a growth factor for early B-cells, is up-ragulated in obese patients with metabolic syndrome and also implicated in generally atherosclerotic-related diseases [34,35]. Furthermore, visfatin has an immunomodulatory effect by increasing the levels of pro-inflammatory cytokines such as TNF-α and IL-6 [36]. According to the report of Derdemezis et al. [37], visfatin secretion was inhibited by quercetin in human Simpson-Golabi-Behmel syndrome (SGBS) adipocytes. In our study, we did not find significant differences in the plasma levels of visfatin after 12 weeks of OPE supplementation. Indeed, Kim et al. [14] also reported that quercetin-rich OPE did not alter the mRNA levels of visfatin from mesenteric fats.

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Unlike TNF-α, a potent inflammatory marker, IL-4 is the biologic anti-inflammatory mediator. It is known to originate from T-cell and plays biologic anti-inflammatory roles through inhibition of the production and release of pro-inflammatory mediators such as TNF-α [38]. In the present study, we observed that placebo or OPE supplementation increased plasma IL-4 levels without statistically significant differences between the two groups.

To the best of our knowledge, no previous human study investigated the effects of quercetin-rich OPE on inflammatory mediators in obese women. There are several reasons that may explain the lack of effects on these modulators of systemic inflammation. First, the anti-inflammatory properties of quercetin or quercetin-rich OPE are clearly seen in in vitro studies and these effects are also different between results from human and animal studies which may associated with difference of physiology in humans and animals as well as difference in the levels of inflammation status. In addition, there are only few studies examined the effect of OPE supplementation in humans. Second, although the participants of this study were overweight and obese, most of them were relatively healthy individuals with very low levels of inflammation since subjects with hypertension or diabetes were excluded from this study. The effect of OPE supplementation may be more visible in individuals with high levels of inflammation. Third, our 12-week administration of OPE was probably not long enough to find differences in the inflammatory mediators production. In addition, a large biological variation in measured parameters, evident from high standard deviations reduced the power to detect significant changes in the inflammatory mediators. Furthermore, we observed a significant reduction in the PBFM and an increase in adiponectin concentration in the placebo group which may occur due to the psychological effect of placebo intake.

In conclusion, our findings demonstrated that 12-week supplementation of OPE did not affect modulators of systemic inflammation in overweight and obese women. We could not find any significant adverse effect of OPE supplementation on the hepatic biomarkers such as AST and ALT compared with placebo. It seems that further studies are required with various doses of OPE and/or a large number of subjects to determine the effect of OPE supplement on the inflammation more extensively.

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