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Effects of Quercetin on Adiponectin-Mediated Insulin Sensitivity in Polycystic Ovary Syndrome: A Randomized Placebo-Controlled Double-Blind Clinical Trial

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ABSTRACT

Polycystic ovary syndrome (PCOS) is a heterogeneous, multi-causal, and genetically complex disorder, which is related to the failure in endocrine glands. Adiponectin has been reported to be low in PCOS, even in the absence of adiposity. Quercetin reduces serum glucose, insulin, triglycerides, and cholesterol levels and increases the expression and secretion of adiponectin. The aim of this study was to determine the effect of quercetin on the adiponectin-mediated insulin sensitivity in PCOS patients. Eighty-four women with PCOS were selected and randomly assigned to 2 groups of treatment and control. The treatment group received 1 g quercetin (two 500 mg capsules) daily for 12 weeks, and the control group received placebo. In addition to anthropometric assessments, fasting serum levels of total adiponectin, high-molecular-weight (HMW) adiponectin, glucose, insulin, testosterone, LH, and SHBG were also measured at the baseline and at the end of the trial. Quercetin could slightly increase the level of adiponectin by 5.56 % as compared to placebo (adjusted p-value = 0.001) and HMW adiponectin by 3.9 % as compared to placebo (adjusted p-value = 0.017), while it reduced the level of testosterone (0.71 ng/dl in quercetin vs. 0.77 ng/dl in placebo; p < 0.001) and LH (8.42 IU/l in quercetin vs. 8.68 IU/l in placebo; p = 0.009). HOMA-IR levels were also significantly (p < 0.001) lower in quercetin (1.84) group compared to placebo group (2.21). Oral quercetin supplementation was effective in improving the adiponectin-mediated insulin resistance and hormonal profile of women with PCOS.

Introduction

Polycystic ovary syndrome (PCOS) is a complex disorder characterized by infertility, hirsutism, obesity, and various menstrual disturbances (e. g., oligomenorrhea, amenorrhea, and anovulation). Nowadays, PCOS is recognized as a metabolic syndrome with several symptoms such as dyslipidemia, obesity, high blood pressure, and increased inflammatory factors [1]. Nearly half of women with PCOS have obesity and insulin resistance, which are paramount in the pathogenesis of this syndrome [2].

Reduced adiponectin level in PCOS patients, seem to be associated with the pathogenesis of PCOS and its consequent metabolic complications [3]. Adiponectin is one of the most plentiful adipose-derived factors that exerts beneficial cardiometabolic roles. It improves insulin sensitivity, and exerts anti-atherogenic and anti-inflammatory effects [4]. There is compelling evidence indicating that a decreased adiponectin level is associated with insulin resistance and obesity. Moreover, adiponectin level is low in women

with PCOS, even in the absence of adiposity [5]. Therefore, adiponectin is suggested as a biomarker for PCOS; however, longitudinal studies are needed to better understand the possible causal pathways. Several oligomeric forms of adiponectin with different biological activities have been discovered in serum, including low molecular weight (LMW) complexes, hexamers, and high molecular weight (HMW) multimers. Previous studies have shown that the ratio of HMW adiponectin to total adiponectin is highly correlated with insulin sensitivity indices [6]. Interestingly, testosterone selectively inhibits secretion of HMW adiponectin by adipocytes [7], which supports the hypothesis of hyperandrogenism-mediated decreased HMW adiponectin levels in women with PCOS [8].

Quercetin is a well-recognized natural compound with antioxidant and anti-inflammatory roles [9]. Its beneficial effects on metabolic syndrome, obesity, and insulin resistance have been studied [10, 11]. Flavonoids, which are abundantly found in plants, are currently among the most attractive agents in controlling and prevention of diseases such as diabetes and metabolic syndrome [12]. Complementary feeding of diabetic mice with this flavonoid had resulted in amelioration of dyslipidemia, hypertension and hyperinsulinemia, as well as reduction in TNF-α production and weight loss [13]. In another study on mice, it was demonstrated that high calorie diet with concomitant administration of quercetin lowered the levels of glucose, insulin, triglycerides, and cholesterol but increased the secretion of adiponectin [14]. Quercetin is able to inhibit nuclear factor-κB (NF-κB), which theoretically might prevent the synthesis of TNF-α and subsequently lead to increasing the production of adiponectin [15] The study by Egert et al. reported the bioavailability of quercetin oral supplementation in healthy human subjects as 150 mg, which can increase plasma concentration of quercetin 570 % [16].

Considering the importance of adiponectin in PCOS and the beneficial effects of quercetin, this flavonoid may be effective in the treatment of PCOS. However, to our knowledge, the efficacy of quercetin administration in amelioration of PCOS and its associated insulin resistance have not been studied yet. Hence, this study was aimed to investigate the effects of quercetin on the total serum level of adiponectin, HMW adiponectin, insulin resistance, and some other important factors in women with PCOS.

Materials and Methods

Trial design

Subjects with PCOS were randomly allocated into 2 groups receiving either quercetin supplement (treatment) or placebo (control), in a parallel group (1:1) single-center design. The study protocols were approved by the Ethical Committee of Tehran University of Medical Sciences. The registration ID of this study in Iranian Registry of Clinical Trials was IRCT2013112515536N1.

Participants

Eighty four women diagnosed with PCOS according to the 2003 Rotterdam criteria [17] were voluntarily recruited from Arash Hospital, Tehran, Iran from January 2014 to January 2015. All women were 20–40 years old and had the Body Mass Index (BMI) of 25–40 kg/m^2. The patients were enrolled if they did not have simultaneous endocrine and metabolic diseases such as hypo- or hyperthyroidism, androgen secreting tumors, diabetes mellitus, adrenal hyperplasia, and Cushing's syndrome. The patients who had been prescribed with interfering medicines such as metformin, contraceptive, antihypertensive, fat-lowering, or anti-inflammatory drugs were also excluded. All the recruited patients were informed of the purpose of the study, and completed a written informed consent. They were free to discontinue the trial at any time during the study.

Interventions

The present randomized, placebo-controlled, double-blind clinical trial consisted of a 12-week treatment with quercetin or placebo. The treatment group (n = 42) was given 1 g quercetin (Jarrow, USA) daily in the form of two 500 mg capsules after each main meal (breakfast and lunch) for 12 weeks. The placebo group (n = 42) was given 2 capsules containing starch for 12 weeks. Placebo capsules were similar to quercetin capsules regarding appearance, and were produced in the School of Pharmacy, Tehran University of Medical Sciences. The compliance of the volunteers with the study protocol was monitored by counting returned capsules every 2 weeks. Both groups were told to maintain their diet and physical activity during the study. Based on the previous studies, the duration of quercetin therapy was chosen for 12 weeks [18, 19]. Oral quercetin, in human, is safe at gram doses. We know that the most effective dose of quercetin on glycemic status is 60 mg/kg, approximately equivalent to 4 g for an adult human [20]; however, quercetin supplementation has been demonstrated to exert its beneficial effects in human even with lower doses (e. g., 500 mg/daily and 1 000 mg/daily) [20–22]. A duration more than 4-weeks of supplementation has been suggested for the initiation of quercetin effects [20–22].

Outcomes

Changes in serum adiponectin and HMW adiponectin levels were the primary outcomes of this trial. Anthropometric, metabolic, and hormonal profiles were also assessed.

A questionnaire was used to gather necessary data about each participant. We measured body weight by a scale (Seca, Germany) while the patients wore no shoes and had light clothing. Height was measured by a mounted tape while patients wore no shoes. BMI was obtained as the weight in kilograms divided by the square of the height in meters. Waist circumference (WC) and hip circumference (HiC) were measured using a soft tape in standing position. Waist was considered as the narrowest circumference between the costal margin and the iliac crest, and hip as the widest circumference between the waists and tight. Waist to hip ratio (WHR) was calculated as Waist circumference (WC) in centimeters divided by hip circumference (HiC) in centimeters. A sphygmomanometer (Rester) was used to assess systolic blood pressure (SBP) and diastolic blood pressure (DBP) in a sitting position and after 5–10 min rest. The blood sampling (10 ml) was performed between 7 and 9 AM, after 12 h of fasting. The serum was separated by centrifugation, and then stored at − 80 °C until further analysis. Serum adiponectin (Crystal, China) and serum HMW adiponectin (Cusabo, China) levels were measured by enzyme-linked immunosorbent assay (ELISA) method.

Serum glucose was measured by the standard enzymatic method with commercially available kit (Pars Azmun, Tehran, Iran). Serum insulin level was also determined using ELISA method (Monobind. USA). HOMA-IR, which was used as an index of insulin resistance, was calculated by the following formula [23]:

$$\text{HOMA-IR} = \frac{\text{Fasting insulin}\,(\mu\text{U/ml}) \times \text{Fasting glucose}\,(\text{mmol/l})}{22.5}$$

The serum concentration of testosterone and SHBG was measured by direct immunoenzymatic assay (DiaMetra, Italy) using an ELISA Reader (Statfax 2600, USA). Also, the serum concentration of LH was determined by electrochemiluminescence immunoassay (Roche, Indianapolis, IN, USA). Intra- and inter-assay coefficient of variation of the kits were < 8 and < 10 %, respectively.

Sample size

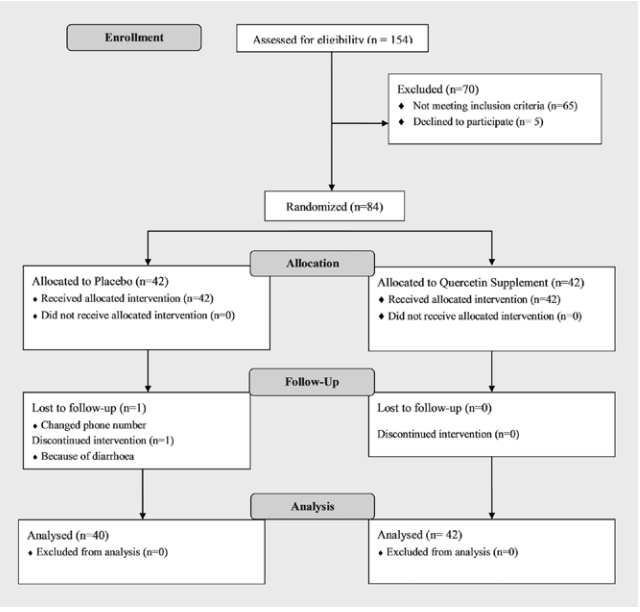
Total adiponectin and HMW adiponectin were selected as the primary outcome variables. To determine the considerable effect size for their changes based on previous studies, the mean differences between patients with PCOS and healthy subjects regarding these variables were recorded (total adiponectin 2.5 ng/ml, and HMW adiponectin 1.4 ng/ml) [8]. Half of the previously observed mean differences (total adiponectin 1.25 ng/ml, and HMW adiponectin 0.7 ng/ml) was selected as the effect size. It means that if the supplement was able to change adiponectin levels even as half of the difference between the PCOS and healthy individuals, we would consider it as clinically acceptable change. Also, based on the previous studies [8], standard deviations for total adiponectin and HMW adiponectin were considered as 1.81 and 1.76, respectively. The probability of type one error was considered as 0.05, and power of 80 % was selected. The required sample size was determined as 34 patients per group for total adiponectin and 40 patients per group for HMW adiponectin, respectively. The higher sample size (40) with 5 % loss to follow-up rate resulted in 42 patients per group for this trial.

Randomization

The subjects were randomly assigned through permuted blocked randomization (size = 4) to receive either quercetin or placebo. A blinded statistician provided sequentially numbered containers for concealment. One staff of the Arash Hospital's PCOS clinic, who was also blinded, provided the subjects with the sealed sequentially numbered containers. The physicians, who were also blinded, explained the interventions to the participants and followed their adherence by weekly calls and counting the returned capsules every 2 weeks.

Statistical analysis

Continuous variables are presented as mean (SD). Independent t-test was used to compare the means of continuous variables between the 2 groups. We used analysis of covariance (ANCOVA) to compare the means of post-intervention continuous outcomes between the 2 groups by adjustment on pre-intervention results. Statistical analyses were performed using SPSS 20.0 software (IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp). p-Values less than 0.05 were considered statistically significant.



▶ **Fig. 1** The entire study process diagram.

▶ **Table 1** Baseline characteristics of the study participants.

Baseline characteristics	Quercetin (n = 42)	Placebo (n = 40)	p-Value *
Age (years)	29.45 (4.09)	30.00 (5.44)	0.607
Weight (kg)	76.46 (11.89)	74.89 (11.74)	0.550
Height (cm)	161.17 (5.11)	161.68 (4.46)	0.633
BMI (kg/m^2)	29.32 (3.71)	28.61 (4.06)	0.411
WHR	0.83 (0.02)	0.83 (0.02)	0.233
SBP, Mean (SD)	126 (6.6)	126 (6.7)	0.644
DBP, Mean (SD)	88 (7.2)	84 (6.4)	0.018 *

All values are Mean (SD). * Significances are based on Independent *t*-test

BMI: Body mass index; WHR: Waist to hip ratio; SBP: Systolic blood pressure; DBP: Diastolic blood pressure

Results

The entire process of this study including the selection and number of samples, and follow-up steps are shown in ▶ **Fig. 1**. Each group contained 42 patients, but 2 individuals from placebo group discontinued the trial. The baseline characteristics of the 2 groups are shown in ▶ **Table 1**. All the anthropometric features were similar in the studied groups except for diastolic blood pressure (DBP).

▶ **Table 2** shows the comparison of post-intervention anthropometric features between the 2 groups, analyzed by independent t-test (the crude condition) and ANCOVA. The results showed that

▶ **Table 2** Post-intervention anthropometric characteristics of women with PCOS.

	Quercetin (n = 42)	Placebo (n = 40)	p-Value[1]	Adjusted p-value[2]
Weight (kg)				
Baseline	76.46 (11.89)	74.89 (11.74)	0.505	0.085
Endpoint	76.13 (11.98)	74.82 (11.70)	0.618	
p-Value[3]	< 0.001	0.293		
BMI (kg/m^2)				
Baseline	29.32 (3.71)	28.61 (4.06)	0.411	0.054
Endpoint	29.19 (3.73)	28.59 (4.04)	0.485	
p-Value[3]	< 0.001	0.289		
WHR				
Baseline	0.83 (0.02)	0.83 (0.02)	0.233	0.107
Endpoint	0.83 (0.02)	0.83 (0.02)	0.584	
p-Value[3]	0.028	0.05		

All values are mean (SD). [1]Between group p-values, [2]Between group p-values based on ANCOVA with variables age, DBP, SHBG, and baseline value of each variable as covariates, [3]Within group p-values

BMI: Body mass index; DBP: Diastolic blood pressure; SHBG: Sex hormone-binding globulin

the crude and adjusted post-intervention values of BMI, WHR, and weight were not significantly different between the 2 groups.

Quercetin could significantly increase adiponectin by 8.6 % ($p < 0.001$) and HMW adiponectin by 7.4 % compared to baseline ($p < 0.001$), while placebo did not significantly increase their levels. Between-group analysis showed significant differences between the placebo and quercetin interventions with regard to adiponectin and HMW adiponectin after adjustment for baseline covariates (▶ **Table 3**). Moreover, quercetin supplementation could slightly decrease testosterone and LH levels, while they remained unchanged in the placebo group. Testosterone and LH levels were also different between the 2 groups ($p < 0.01$) after adjustment for baseline covariates (▶ **Table 3**). The effect of quercetin on SHBG was marginal.

Regarding insulin resistance, the quercetin group was observed to have a significantly decreased HOMA-IR (17.5 %, $p < 0.001$), but such improvement was not observed in the placebo group. After controlling for important factors including age, DBP, and SHBG and the baseline values of each variable as covariates, these metabolic characteristics showed significant difference between the 2 groups (▶ **Table 4**).

Significant inverse correlations were found between the fold changes of HOMA-IR and serum total adiponectin (Spearman's $\rho = -0.385$, $p < 0.001$) and HMW adiponectin (Spearman's $\rho = -0.347$, $p = 0.001$). Significant inverse associations was also observed between the changes in adiponectin and BMI (Spearman's $\rho = -0.372$, $p < 0.001$), and WC (Spearman's $\rho = -0.231$, $p = 0.018$).

Fig. 1S shows the correlation of fold changes of adiponectin with HOMA-IR, BMI, WHR, and WC by the intervention groups. It is obvious that the majority of individuals with decreased HOMA-IR, BMI, and WC and the increased adiponectin belong to the quercetin group. To further confirm this finding, we defined a categorical variable (having improvements for HOMA-IR AND serum total AND HMW adiponectin). **Table 1S** shows a significant ($p < 0.001$, $\chi^2 = 14.114$) association between quercetin supplementation and improvements of these variables. Number needed to treat was 2.43 (95 % CI = 2.39–2.47).

Discussion

The results of the present research showed that quercetin supplementation might be an advantageous option for PCOS as the most prevalent endocrinopathy in women. We observed a somewhat favorable effect of quercetin on PCOS by increasing the adiponectin and HMW levels. It also reduced the HOMA-IR and slightly improved the hormonal profile of the participants.

Quercetin is one of the commonly referred flavonoids with antioxidant and anti-inflammatory properties. This flavonol is found in some foods such as apple, onion, tea, and red wine; it induces the release of nitric oxide and reduces free radicals [24]. Some studies have previously demonstrated the beneficial antihypertension and anti-atherosclerosis properties of quercetin in human [25]. Supplementation with quercetin has been accompanied by decreased TNF-α production and improvement of dyslipidemia, hypertension, and hyperinsulinemia, as well as weight loss in diabetic mice [26]. Studies on mice demonstrated that quercetin lowered the levels of glucose, insulin, triglycerides, and cholesterol, but increased the secretion of adiponectin [26, 27].

The results of this study revealed that quercetin is able to increase total and HMW adiponectin levels without changing BMI and WHR (▶ **Table 2**). Quercetin has been shown to induce adiponectin secretion in adipocytes through a PPAR-γ-independent pathway [28]. Thus, the increased adiponectin level following quercetin administration seems to be a direct effect of this flavonoid and not

▶ **Table 3** Post-intervention adiponectin and high-molecular weight adiponectin serum levels, and hormonal profile of women with PCOS.

	Quercetin (n = 42)	Placebo (n = 40)	p-Value[1]	Adjusted p-value[2]
Adiponectin (ng/ml)				
Baseline	9.58 (1.80)	10.05 (1.24)	0.163	0.001 *
Endpoint	10.40 (1.96)	10.25 (1.41)	0.686	
p-Value[3]	< 0.001	0.062		
HMW (ng/ml)				
Baseline	5.12 (1.01)	5.30 (0.91)	0.421	0.017 *
Endpoint	5.50 (1.03)	5.42 (0.90)	0.734	
p-Value[3]	< 0.001 *	0.037 *		
Testosterone (ng/ml)				
Endpoint	0.71(0.15)	0.76 (0.12)	0.09	< 0.001 *
Baseline	0.78 (0.16)	0.78 (0.15)	0.941	
p-Value[3]	< 0.001 *	0.260		
LH (mIU/ml)				
Endpoint	8.29 (2.99)	8.83 (2.00)	0.326	0.009 *
Baseline	8.40 (3.03)	8.67 (2.07)	0.644	
p-Value[3]	0.013 *	0.050		
SHBG (nmol/l)				
Baseline	41.04 (17.73)	35.62 (13.04)	0.120	0.234
Endpoint	41.36 (2.74)	35.54 (2.08)	0.096	
p-Value[3]	0.033	0.709		

All values are mean (SD). [1]Between group p-values, [2]Post-intervention. Between group p-value based on ANCOVA with variables age, BMI, DBP, SHGB, and baseline value of each variable as covariates, [3]Within group p-values. * Statistically significant ($p < 0.05$). BMI: Body mass index; DBP: Diastolic blood pressure; HMW: High molecular weight; SHBG: Sex hormone binding globulin; LH: Luteinizing hormone

secondary to the altered adiposity [29]. Different doses of quercetin have been effective in reducing HOMA-IR [30]. Quercetin also reduces the waist circumference and triglycerides in metabolic syndrome patients [31]. In line with previous studies [23, 32], an inverse correlation between HOMA-IR and adiponectin was observed. Additionally, the post-supplementation concurrent improvements of HOMA-IR, serum total and HMW adiponectin indicates an adiponectin-mediated insulin-sensitizing effect for quercetin (**Fig. 1S**, and **Table 1S**).

The relationship between adiponectin and PCOS has been reviewed by Groth (2010), suggesting that adiponectin derangement is attributed to insulin resistance and adiposity [5]. In women with PCOS, the level of adiponectin is lower even in the absence of adiposity. In a cross-sectional study by Tao et al. (2013), in which the levels of total and high molecular weight (HMW) adiponectin and their relation to insulin resistance were investigated, it was demonstrated that total and HMW adiponectin levels were significantly lower in PCOS patients compared to healthy women [33]. In addition, HMW adiponectin showed a strong correlation with insulin resistance predictive model. They showed that the reductions in HMW adiponectin were associated with increased HOMA-IR in healthy women and those with PCOS [33, 34]. Toulis et al. confirmed the previous results suggesting that adiponectin levels are reduced in PCOS [35]. They believed that the lower serum levels of adiponectin in these patients are probably associated with insulin resistance, but independent of testosterone [35]. In a cross-sectional study by Wickham et al., investigating the levels of total and HMW adiponectin, it was shown that the levels of SHBG, insulin, FBS, WHR, testosterone, and total and HMW adiponectin are lower in PCOS women compared to healthy women [8]. They further suggested that total and HMW adiponectin are inversely correlated with WHR and testosterone, and positively correlated with insulin sensitivity. Finally, they stated that changes in HMW adiponectin levels in women with PCOS might contribute to the insulin resistance intrinsic to the syndrome [8, 36]. Therefore, the favorable effects of quercetin on insulin resistance parameters that were observed in the present study may be related to its effect on adiponectin alterations.

Our findings showed that supplementation with quercetin have slightly beneficial effects on testosterone and LH level, which are the important hormones in the pathogenesis of PCOS. It has been shown that adiponectin modulates the reproductive system by inhibiting LH and GnRH secretion [37]. Adiponectin receptors are expressed in oocytes and animal studies have demonstrated that this protein exerts its protective functions on oocytes through AMPK pathway [38]. Quercetin administration did not have a significant influence on SHBG levels, indicating that the effect of quercetin on testosterone is not secondary to the changes in SHBG levels. To date, the effects of quercetin on testosterone levels have not been

▶ **Table 4** Post-intervention metabolic profile of women with PCOS.

	Quercetin (n = 42)	Placebo (n = 40)	p-Value[1]	Adjusted p-value[2]
Insulin (μU/ml)				
Baseline	10.09 (2.78)	9.91 (2.56)	0.754	< 0.001 *
Endpoint	8.45 (2.23)	9.81 (2.62)	0.013 *	
p-Value[3]	< 0.001 *	0.279		
FBS (mg/dl)				
Baseline	91.57 (6.74)	89.83 (6.36)	0.231	0.045 *
Endpoint	90.36 (1.03)	89.45 (0.98)	0.526	
p-Value[3]	< 0.001 *	0.083		
HOMA-IR				
Baseline	2.28 (0.72)	2.20 (0.68)	0.604	< 0.001 *
Endpoint	1.88 (0.56)	2.17 (0.69)	0.039 *	
p-Value[3]	< 0.001 *	0.243		

All values are mean (SD). [1]Between group p-values, [2]Between group p-value based on ANCOVA with variables age, DBP, SHBG, and baseline value of each variable as covariates, [3]Within group p-values

* Statistically significant ($p < 0.05$)

BMI: Body mass index; DBP: Diastolic blood pressure; SHBG: Sex hormone binding globulin; HOMA-IR: Homeostasis model assessment-insulin resistance; FBS: Fasting blood sugar

addressed; this study, for the first time, reveals slightly decreased testosterone levels in serum after quercetin supplementation.

Quercetin is a compound with 2 different activities, which are dependent on its dosage as a phytoestrogen. By interaction of quercetin with the estrogen receptor (G-protein-coupled receptor 30), TNF-α will be produced by macrophages through Toll-like receptor 4 (a proinflammatory activity). TNF-α, which is released by macrophages of the adipose tissue, induces IL-6 secretion from the adipocytes. Evidence suggests that TNF-α elevation has an inverse effect on testosterone level and leads to its decline [39].

This study has some limitations as we could not measure quercetin levels in blood and determine its bioavailability. Moreover, clinical characteristics of PCOS (e. g., oligomenorrhea, hirsutism, etc.) were not assessed as outcomes of the current clinical trial, which are needed to be tested in long-term follow-ups. However, no adverse outcomes or aggravations were reported in the present trial after supplementation with quercetin.

Conclusion

The results of the present study showed that supplementation with quercetin leads to elevation of adiponectin and reduction of HOMA-IR, testosterone, LH, FBS, and insulin levels in PCOS patients. The somewhat promising effects of quercetin in PCOS, especially on adiponectin and HMW adiponectin levels, suggest that this flavonoid may offer a valuable supplement for PCOS.

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Conflict of Interest

The authors declare no conflict of interest.

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