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Original Article

Effects of cinnamon supplementation on antioxidant status and serum lipids in women with polycystic ovary syndrome

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ABSTRACT

Background: The objectives of study were to investigate the effects of cinnamon supplementation on antioxidant status and serum lipids in women with polycystic ovary syndrome (PCOS).
Methods: This double-blind randomized controlled clinical trial was conducted on 84 overweight or obese PCOS patients; aged 20–38 years. Subjects in cinnamon (n = 42) and placebo (n = 42) groups were given 3 cinnamon capsules (each one contained 500 mg cinnamon) or placebo daily for 8 weeks. Fasting blood samples, anthropometric measurements and dietary intake data were gathered at the beginning and at the end of the study. Independent t test, paired t test and analysis of covariance were used to analyze of data.
Results: Cinnamon significantly increased serum total antioxidant capacity (P = 0.005). Malondialdehyde was significantly decreased compared with placebo (P = 0.014). Cinnamon supplementation significantly improved serum level of total cholesterol, low-density lipoprotein cholesterol and high-density lipoprotein cholesterol (all P < 0.05). No significant effect was detected on serum triglyceride level.
Conclusions: Cinnamon supplementation improved antioxidant status and serum lipid profile in women with PCOS and may be applicable for reducing PCOS risk factors.

1. Introduction

Polycystic ovary syndrome (PCOS) is a common metabolic and reproductive condition in women with an estimated prevalence of 6% to as high as 26%.[1,2] This disorder is accompanied with irregular menstrual cycle, chronic anovulation and hyperandrogenism. PCOS is associated with complications in different health aspects, including obesity, insulin resistance, infertility, diabetes and atherosclerosis.[3] Oxidative stress (OS) as one of the main causes of molecular damage to cellular is increased in women with the PCOS. Obesity and insulin resistance play a vital role in the pathogenesis of PCOS and subsequently increased OS in these patients. In addition, the resultant oxidative stress induces an inflammatory environment furthering elevated insulin resistance and contributing to hyperandrogenism,[4] dyslipidemia, hypertension and etc.[5,6] Numerous investigations have revealed that oxidative stress level is significantly increased in patients with PCOS compared with the normal ones. Fenkci et al revealed that patients with PCOS had higher OS and increased OS is related to hyperandrogenism status.[7] In another study, Desai et al displayed that the OS is also present in non-obese women with PCOS.[8]

PCOS is a condition with a significant decrease in serum antioxidant. Therefore, antioxidant supplementation may be effective in these patients. Antioxidants are considered significant agents in the

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healthy body. Many studies have displayed that the use of antioxidants, as well as herbal agents, might help to reduce OS.[9] Furthermore, medicinal herbs are expected to have a similar degree of efficacy without the side effects related to conventional medication.

Cinnamomum zeylanicum, is an herbaceous plant, belonging to the Lauraceae family. It is one of the most important spices used by people all over the world. Different flavonoids and Polyphenols isolated from cinnamon have free-radical-scavenging activities and antioxidant properties.[10] These compounds have been revealed to decrease oxidative stress in a dose-dependent manner through the inhibition of 5-lipoxygenase.[11] Antihyperlipidemic and antioxidant activity of cinnamon has been proven in experimental studies.[12–17] In animal study, Shalaby et al indicated that consumption of cinnamon aqueous extract improved activity of tissue antioxidant enzymes in obese diabetic rat.[18] Additionally, in the study by Kim et al, cinnamon lowered total cholesterol and triglyceride levels in diabetic mice.[19] Roussel et al showed that supplementation of 250 mg/day of an aqueous extract of cinnamon increased the plasma levels of thiol group and decreased malondialdehyde compared to those of placebo in patients with impaired fasting blood glucose for 12 weeks.[20]

Although some studies have reported the effects of cinnamon on oxidative stress and lipids profile in several diseases,[5,6,21] Its possible effects on serum antioxidant status and lipids profile of women with PCOS have not been studied. Therefore, we initiated a study to assess the effects of cinnamon supplementation on oxidative stress including serum total antioxidant capacity (TAC), malondialdehyde (MDA) and lipids in women with PCOS.

2. Material and methods

2.1. Design study

A total of 84 women with PCOS aged 20–38 years with a BMI between 25–40 kg/m^2 were enrolled in this double-blind, randomized, controlled clinical trial from the Gynecology clinic, Mohheb Yas Hospital in Tehran, Iran from October 2015 to February 2016. The sample size was determined based on the information acquired from the study by Kort et al for IR.[22] Considering 95% confidence interval and 80% power, the sample size was computed to be 32 per group. This number was increased to 42 per group to accommodate the anticipated dropout rate.

The diagnosis of PCOS was established according to 2003 Rotterdam criteria, which require at least two of three features for diagnosis: chronic amenorrhea or oligo-amenorrhea, clinical and/or biochemical features of hyperandrogenism and polycystic ovaries by ultrasonography.[1] Study exclusion criteria included: thyroid disorders, hyperprolactinemia, diabetes mellitus, pregnancy and lactation, liver or kidney diseases, Cushing syndrome, cardiovascular diseases, seizure and cerebrovascular disorder, hypertension, the use of medications such as insulin sensitizers, insulin, B-blockers, cholesterol-lowering drugs and dietary supplements, smoking, current treatment of infertility, inhaled corticosteroid use, following a specific diet and regular exercise (>2 weeks) and allergy to cinnamon. The Ethical Committee of Tabriz University of Medical Science approved the study protocol and was registered on the Iranian Registry of Clinical Trials website (identifier: IRCT201508173664N14). Written informed consent was gained from each subject. The participants were randomly allocated into two groups using a block randomization procedure with matched subjects in each block based on age and BMI. Subjects were questioned to continue their usual dietary intakes and physical activity during the study.

A general questionnaire was completed for each patient. Body weight was measured using a scale (Seca, Hamburg, Germany), without shoes and wearing light clothing. Height was measured using a mounted tape without shoes. BMI was calculated as the weight in kilogram divided by the height in meters squared. Information about daily energy and macronutrient intakes were obtained by 24-h recall method for 3 d, including 2 d during the week and 1 during the weekend. A three day average for energy and macronutrient intakes of all subjects was analyzed by Nutritionist 4 software (First Databank Inc., San Bruno, CA).

Cinnamon bark was provided from the Iranian Institute of medicinal plants, Tehran, Iran. Cinnamon barks were grinded with a plant tissue grinder. Each capsule containing approximately of 500 mg cinnamon powder was manufactured on October 2015. Subjects in the treatment group received three capsules of cinnamon and control group subjects received three placebo capsules (wheat flour) that they were required to take daily for 8 weeks. The compliance of the volunteers with the study protocol was monitored via phone interviews once per week and also by counting returned capsules every 2 weeks.

2.2. Blood sampling and biochemical assays

Blood samples (5 ml) were collected after a 12-h overnight fasting, in the morning. The serum samples were separated from whole blood by centrifugation at 2606.8 $\times g$ for 10 min (Beckman Avanti J-25; Beckman Coulter, Brea, CA, USA). The serum samples were frozen immediately at −70 °C until assay. Serum total cholesterol (TC), triacylglycerol (TG) and high-density lipoprotein cholesterol (HDL-C) were measured using the standard enzymatic methods by Pars Azmun kit (Karaj, Iran). Low-density lipoprotein cholesterol (LDL-C) concentration was determined by the Friedewald formula: LDL − C = TC − (HDL − C + TG/5).[23] Measurement of TAC in serum was performed by using the colorimetric method with commercial kits (TAC, RANDOX kits; UK).[24–26] The serum MDA level was estimated by using a reaction with thiobarbituric acid as a thiobarbituric acid reactive substance to produce a pink colored complex. Next, its fluorescence intensity was measured at 547 nm with excitation at 525 nm by a spectrofluorimeter (model SFM 25 A; Kontron, Milan, Italy).[27] All anthropometric, dietary intakes, blood sampling and biochemical measurements were assessed again at the end of intervention period in both groups.

2.3. Statistical analyses

The collected data were analyzed using the statistical software SPSS, version 22. (SPSS Inc., Chicago, IL, USA) and the results are expressed as means ± SD. The normality of the distribution of variables was checked by Kurtosis–Skewness test. The baseline measurements and dietary intakes of subjects in two groups were compared using independent samples t test and chi-square test for quantitative and qualitative variables, respectively. Analysis of covariance (ANCOVA) was used to identify any differences between the two groups after intervention, adjusting for baseline measurements and confounders (BMI and energy changes during study). The changes in anthropometric measurements, energy and nutrient intakes and blood parameters of the participants between the beginning and end of the trial were compared by paired samples t test. The percentage of changes in variables after intervention was determined with the formula: [(after values − before values)/before values] × 100. Results with $P < 0.05$ were considered as statistically significant.

3. Results

All of the patients (42 patients in cinnamon group and 42 patients in placebo group) completed the study (Fig. 1). Compliance

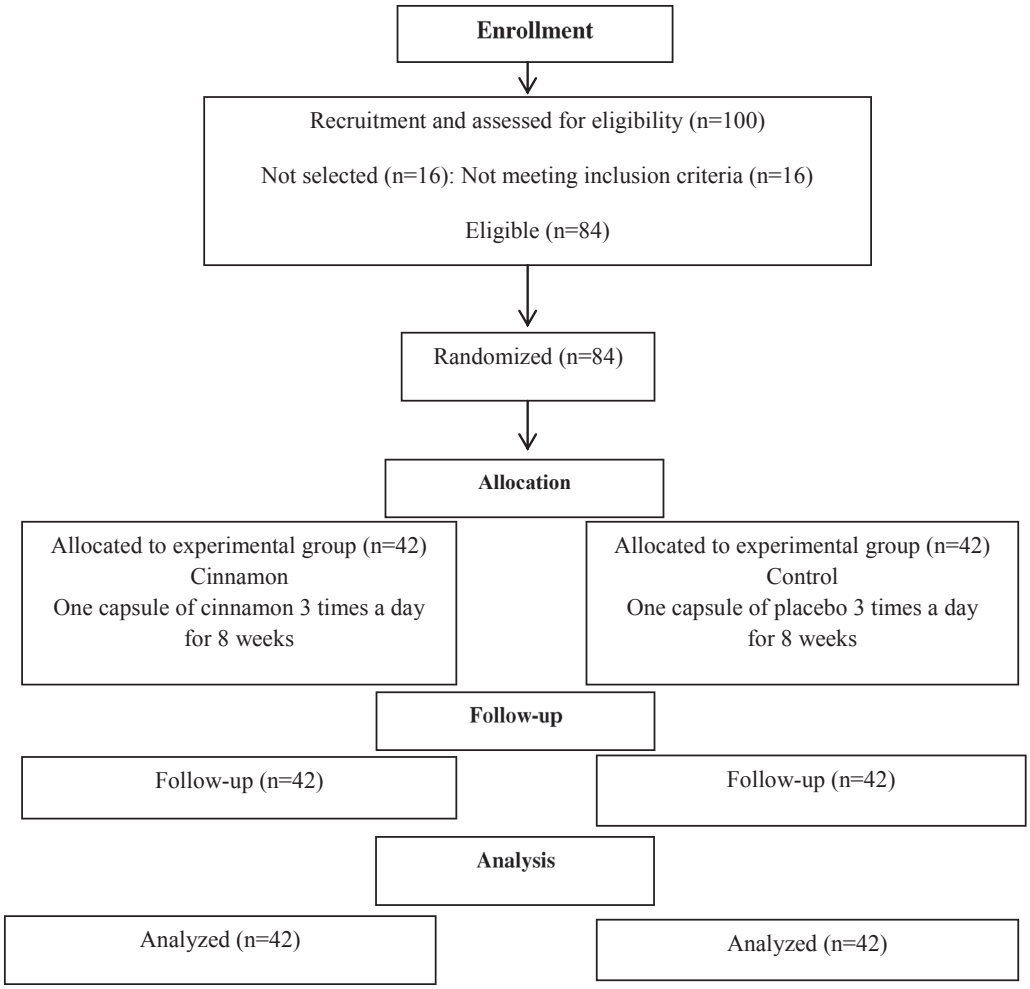

Fig. 1. Participant's flow diagram.

was good, with more than 94% of the supplements prescribed being consumed during the study period. No side effects were reported from participants during study period.

General and biochemical characteristics of participants at the beginning and end of the study are shown in Table 1. There were no significant differences between groups in BMI and daily energy intake in the beginning of the study and after 8 weeks of intervention. Significant differences were seen between the two groups in serum levels of MDA at baseline. Levels of TAC were not different between two groups at baseline. Serum TAC levels significantly change in cinnamon group after intervention compared to their baseline values ($P = 0.001$). Variations in MDA levels were not significant ($P = 0.102$) compare to baseline value. Serum levels of TAC and MDA did not alter significantly in control group. Results of ANCOVA test showed statistically significant differences between two studied groups in serum TAC ($P = 0.005$) and MDA ($P = 0.014$) at the end of the study, adjusted for BMI and energy intake. Serum levels of TAC significantly increased in the cinnamon group by 9.28 % at the end of the study. Significant decrease in serum levels of MDA by 7.87% was obtained in cinnamon group over the 8 week in comparison to baseline values.

Fig. 2(A–D) illustrates changes in serum levels of TG, TC, LDL-C and HDL-C of studied groups and during 8-wk period of study. No significant differences were seen in serum levels of lipids between the two groups at baselines. As shown in Fig. 2(B–D), significant differences were seen between two studied groups in serum levels of TC, LDL-C and HDL-C at the end of the study adjusted for energy, BMI and baseline values ($P < 0.05$). Changes in serum TG ($P = 0.71$) was not significant. (Fig. 2A). Serum levels of TG, TC and LDL-C significantly decreased in the intervention group by 18.24 % (vs. 5.42 % decrease in control group), 7.73 % (vs. 2.10 % decrease in control group) and 10.24 % (vs. 0.63 % decrease in control group), respectively, at the end of the study in comparison to baseline values. (data not shown).

4. Discussion

Cinnamon has been used as a traditional herbal medicine for centuries. This spice has been found to have strong antioxidant, antihyperlipidemia[5] and anti-inflammatory properties. To our knowledge, only few studies revealed antioxidant effects of cinnamon. Based on our literature review, this is the first report concerning the effects of cinnamon consumption on antioxidant status and serum lipid levels in women with PCOS.

Based on results BMI and daily energy intake of subjects did not change significantly in any of groups throughout the study, therefore, these variables could not be accounted as confounding factors in interpreting biochemical findings.

Exposure to endocrine and metabolic disturbances such as hyperandrogenism, hyperinsulinemia and dyslipidemia might be responsible for PCOS-associated oxidative stress.[28] Reactive oxygen species react with lipids causing peroxidative changes that result in

Table 1
General characteristics and antioxidant status of the women with PCOS at baseline and after 8-week of intervention.

variable	Measurement period	Cinnamon group (n = 42)	Control group (n = 42)	MD (95 % CI), p value
Age (y)	Baseline	29.26 (6.14)	30.17 (6.69)	
BMI (kg/m^2)	Baseline	30.75 (5.04)	31.61 (4.84)	
	After intervention	30.62 (4.99)	31.60 (4.87)	
Energy (kcal/d)	Baseline	1651.2(251.09)	1749.3 (265.38)	
	After intervention	1602.4(265.73)	1696 (264.71)	
TAC (mmol/L)	Baseline	1.66 (0.32)	1.79 (0.39)	−0.126 (−0.266 to 0.013), 0.076[a]
	After intervention	1.83 (0.42)	1.73 (0.32)	0.225 (0.06–0.38), 0.005[c]
	MD (95% CI), P-value[b]	0.165 (0.07–0.25), 0.001	−0.055 (−0.18 to 0.07),0.38	
MDA (nmol/mL)	Baseline	2.33 (0.63)	2.06 (0.56)	0.269 (0.006–0.53),0.044[a]
	After intervention	2.16 (0.75)	2.26 (0.73)	−0.385 (−0.68 to −0.08), 0.014[c]
	MD (95% CI), P-value[b]	−0.173 (−0.38 to 0.03), 0.107	0.197 (−0.02 to 0.41),0.07	

BMI body mass index, MDA malondialdehyde, TAC total antioxidant status, MD mean difference, CI confidence interval.
The results are described as means ± Standard Deviation (SD).
[a] MD (95% CI), P-value is reported based on the analysis of independent sample t test.
[b] MD (95% CI), P-value is reported based on the analysis of paired sample t test.
[c] MD (95% CI), P-value is reported based on the analysis of covariance.

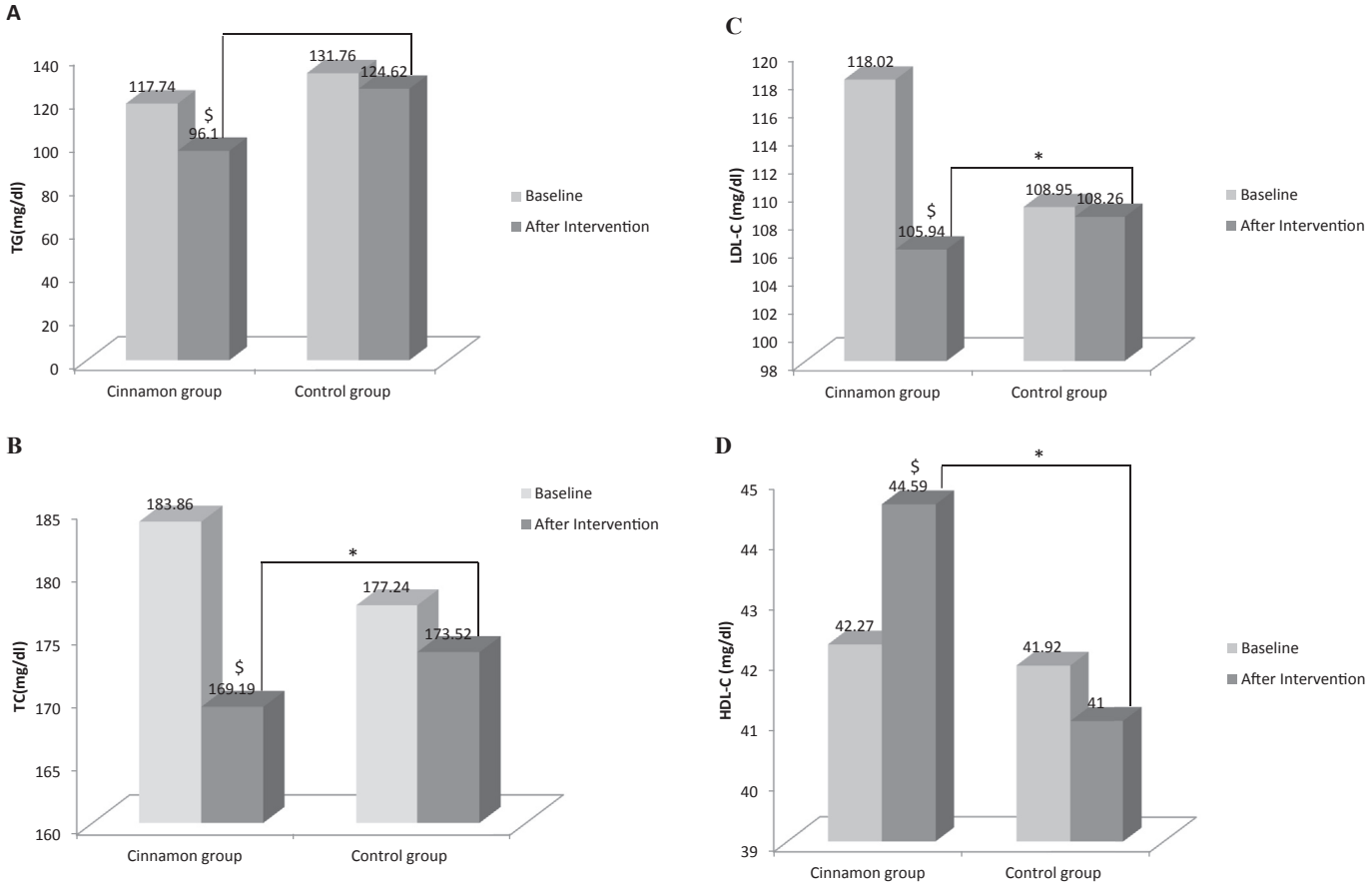

Fig. 2. Effects of cinnamon on (A) triglyceride, (B) cholesterol levels, (C) low density lipoprotein and (D) High density lipoprotein. Data were present as means ± SE for 42 PCOS patients in each group. $^{\$}P < 0.05$ for within group comparisons (paired sample t test); $^{*}P < 0.05$ for between group comparisons (ANCOVA adjusted for baseline value, BMI and energy intake daily).

elevated lipid peroxidation products such as MDA.[29] TAC is an indicator of the overall protective effect of antioxidants in body fluids, on cell membranes and other components of cells against oxidative injury.[30] According to our results, cinnamon supplementation caused a significant increase in TAC levels and decreased MDA levels compared with placebo group. Our findings also were similar with results of other studies.[31,32] Salih indicated that consumption of 1 g/day of cinnamon improved oxidative stress markers among poorly controlled type 2 diabetes patients for 12 weeks.[32] In an experimental study, Sariözkan demonstrated that cinnamon bark oil had protective effect on oxidant/antioxidant balance, in 88 adult diabetic male rats for 10 weeks.[33] Various studies reported that ether, aqueous and metabolic extracts of cinnamon have considerable antioxidant activities.[34,35] Faix et al revealed that considerably lower lipid peroxidation in plasma and duodenal epithelium of chicks fed the diet supplemented with 0.10% of cinnamon essential oil.[36]

It was revealed that cinnamon has high levels of different phytochemicals compounds with free radical scavenger actions, such as

epicatechin, camphene, eugenol, gamma-terpinene, phenol, salicylic acid and tannins.[37] Proanthocyanidins, which are high in cinnamon, are plant metabolites with antioxidant activity.[38] Hence, cinnamon is rich in antioxidants. These components inhibit peroxynitrite-induced nitration and fatty acid as well as lipid peroxidation in the β-carotene-linoleic acid system in vitro models.[35] They display a protective capacity against irradiation induced lipid peroxidation in liposomes and quench hydroxyl radicals and hydrogen peroxide.[39] The ethanolic extract of cinnamon has been demonstrated to decrease the carbon tetrachloride induced lipid peroxidation and as a result, a fall occurs in the markers of oxidative stress such as MDA.[40]

Our results demonstrated that cinnamon supplementation had antioxidant capability and improved the oxidative stress in the studied subjects. It was possible that the elevate in TAC in our cinnamon treated group might be due to their decreased consumption for free radical detoxification or utilization which was approved by following reduction in serum MDA and improvement in TAC levels.

Our findings indicated that supplementation of cinnamon significantly decreased serum levels of TC and LDL-C and increased HDL-C levels. These results are in agreement with findings of some others studies.[41–43] Soliman showed that supplementation with 1.5 g/day and 3 g/day of cinnamon for 45 days, significantly decreased TG, TC and LDL-C levels in patients with type 2 diabetes.[44] Khadem et al showed that 1.5 g/day of cinnamon for 8 weeks, improved lipid profiles in type 2 diabetic patients.[45] In animal study, Sambaiah demonstrated that cinnamon reduced serum TC level in rats even after increasing the intake up to 5 times the normal intake.[46] Quin et al showed that cinnamon administration (50 mg/kg daily) for 8 weeks decreased TG, TC, chylomicron-apoB48 and VLDL-apoB100 in Wistar rats fed on a high-fructose diet to induce insulin resistance.[47] Recent study suggested that cinnamon extract may improve insulin action via increasing glucose uptake, perhaps through enhancing the insulin-signaling pathway in skeletal muscle.[38]

It was proposed that antihyperlipidemic activity of cinnamon might be due to its high contents of polyphenols inhibiting the intestinal absorption of cholesterol with subsequent hypocholesterolemic activity.[18] In another study, cinnamaldehyde changed serum biochemical factors associated with lipolysis, such as glycerol and free fatty acid levels and increased adipose tissue lipolysis in high-fat diet-fed mice.[48,49] Moreover, Kim et al confirmed that cinnamon administration regulated lipid metabolism via the up-regulation of PPARα expression.[19] Sheng et al reported that PPARα expression increased the cellular uptake of fatty acids liberated from fat tissues. PPARα ligands also increased the expression of the lipoprotein lipase gene, resulting in the anti-hyperlipidemia effect.[28] However, some studies did not find any significant change in lipids profile after cinnamon consumption or its different extracts.[50,51]

The strengths of the present study were the double blind placebo-controlled design with no drop-outs. However, our study had some limitations including its short study duration of 8 weeks, small sample population and use of a fixed dose of cinnamon. This study also included subjects with BMI $\geq$ 25 kg/m^2. Therefore, the results of our study may not be applicable to underweight or normal weight patients with PCOS and also to other doses of cinnamon or different intervention period. Studies are warranted to evaluate the effects of cinnamon on androgen status, oxidized LDL and other indicators of OS in these patients, too.

In conclusion, results of present study indicated that 1.5 g of cinnamon supplementation for 12 weeks improved antioxidant status and lipid profile in women with PCOS that could be effective for this disease.

Conflict of interest

The authors declare no conflict of interest.

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