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ABSTRACT

Polycystic ovary syndrome (PCOS) is a heterogeneous clinical syndrome. Recent studies examine different strategies to modulate its related complications. Chlorogenic acid, as a bioactive component of green coffee (GC), is known to have great health benefits. The present study aimed to determine the effect of GC on lipid profile, glycemic indices, and inflammatory biomarkers. Forty-four PCOS patients were enrolled in this randomized clinical trial of whom 34 have completed the study protocol. The intervention group (n = 17) received 400 mg of GC supplements, while the placebo group (n = 17) received the same amount of starch for six weeks. Then, glycemic indices, lipid profiles, and inflammatory parameters were measured. After the intervention period, no significant difference was shown in fasting blood sugar, insulin level, Homeostasis model assessment of insulin resistance index, low-density lipoprotein, high-density lipoprotein, Interleukin 6 or 10 between supplementation and placebo groups. However, cholesterol and triglyceride serum levels decreased significantly in the intervention group (p < 0.05). This research confirmed that GC supplements might improve some lipid profiles in women with PCOS. However, more detailed studies with larger sample sizes are required to prove the effectiveness of this supplement.

Keywords: Dyslipidemia; Glycemic index; Polycystic ovary syndrome; Inflammation



Conflict of Interest

The authors declare that they have no competing interests.

Author Contributions

Conceptualization: Meshkani M; Formal analysis: Meshkani M, Yekaninejad M; Investigation: Meshkani M, Saedisomeolia A; Methodology: Meshkani M; Project administration: Saedisomeolia A; Supervision: Saedisomeolia A; Visualization: Mousavi SA, Ildarabadi A, Vahid-Dastjerdi M; Writing original draft: Meshkani M, Yekaninejad M, Ildarabadi A, Vahid-Dastjerdi M; Writing review & editing: Mousavi SA.

INTRODUCTION

Polycystic ovary syndrome (PCOS) is a complicated endocrine disorder without specific etiology affecting 4–8 percent of women during reproductive age and results in menstrual dysfunction, hirsutism, ovulatory infertility, and some metabolic morbidity [1-3]. Most studies have focused on the development of abdominal obesity, insulin resistance and hyper-insulinemia, glucose intolerance, increased risk of type 2 diabetes mellitus (DM2), dyslipidemia (hyper-triglycridemia and low high-density lipoprotein (HDL) cholesterol) and hypertension which can elevate the risk of atherosclerosis in women with PCOS [4-6].

Inflammation, as another characteristic of PCOS, has been gaining importance recently. Low-grade chronic inflammation is strongly associated with hyperandrogenism and can result in ovarian dysfunction and metabolic aberration [7]. Some evidence claimed the direct simulative role of inflammation on excess androgen production of ovarian [8,9]. Since PCOS is affected by obesity, insulin resistance, and inflammation, dietary interventions and behavioral changes can be proper strategies. Exercise, high-protein moderate-carbohydrate diets, weight loss, anti-obesity pharmacologic agents, or bariatric surgery are different approaches to managing PCOS [10]. Moreover, antioxidants and anti-inflammatory agents have been shown to improve metabolic conditions related to PCOS, especially insulin resistance [11,12]. Medical management, such as contraceptive pills, metformin, and hormone therapy, were presented for PCOS patients; although, non-benefit in some circumstances and side effects cause researchers to pursue other effective therapeutic strategies [13]. Recently, attention to complementary medicine and nutritional supplements gain increased as therapeutic strategies in chronic disease with high efficacy and fewer side effects [14-24]. Green coffee (GC) belongs to the genus of coffee (Rubiaceae family), is a significant source of chlorogenic acids (CGA), and has different biological effects. Recent evidence in humans and animals demonstrated vasoreactivity improvement, antihypertensive effect, body weight loss, and modulation of glycemic indices from GC bean extract [25-27]. For instance, in a clinical trial, Roshan et al. examined the effect of GC (800 mg/day) in patients with metabolic syndrome for eight weeks [28]. They observed a positive impact of GC on some metabolic syndrome components such as high fasting blood glucose, insulin resistance, and abdominal obesity [28]. Another clinical trial study compared the administration of 40 g/day of green or black coffee in healthy subjects [29]. A significant reduction was observed regarding body weight and body mass index (BMI) with GC compared with black coffee. Also, waist circumference and abdominal fat were reduced after both interventions [29]. Considering the effective role of GC in the pathways involved in the pathogenesis of PCOS, including improving insulin resistance [30], blood sugar [30], weight [31,32], and anti-inflammatory [33] and antioxidant effects [34], and the lack of a study that examines these effects in patients with PCOS, this study aimed to evaluate the effect of GC supplement on lipid profile, glycemic indices, and inflammatory biomarkers.

MATERIALS AND METHODS

GC supplement characteristics

The main supplement contained 400 mg of standard GC extract (raw) containing more than 50% CGA and low caffeine (less than 2%) as well as small amounts of lactose (Bonyan Salamat Kasra [BSK] Company, Iran). The placebo supplement contained starch similar to the original supplement in size, shape, weight, and color.



Study design

The study was a double-blind, randomized clinical trial (RCT) which is approved by the Ethics Committee of Biomedical Research, Islamic Azad University, Science and Technology Branch. The study was registered in the Iranian Registry of Clinical Trials (IRCT), available at http://www.irct.ir (ID: IRCT20180808040745N1). Among the patients whose gynecologist diagnosed and confirmed their disease according to established standards, forty-four women with PCOS who met the inclusion criteria were enrolled in the study. Participants were divided into intervention and placebo groups by randomization block design. The allocation sequence was done by the random allocation software (RAS) (Microsoft Visual Basic 6, http:// www.msaghaei.com/Softwares/dnld/RA.zip, Latest version). To warrant the blinding in the evaluation process, the patients were allocated to the intervention groups by a person who was not involved in the current study. The researchers and patients were unaware of each group's intervention type.

Study sample

Inclusion criteria were women with PCOS that were willing to participate in the study age range of 20–40 years. Exclusion criteria were: having allergies and intolerance to GC supplements, taking steroid and non-steroid anti-inflammatory drugs, thyroid and kidney disorders, nutrition supplements rather than calcium, iron, and folic acid, unwillingness to continue the cooperation of each research unit during the study, acute disorders in during the study period, exposure to acute and severe stress during the study or pregnancy.

Study intervention

After a thorough explanation of the purpose and methods of the study, informed consent was obtained from all participants. Patients were randomly divided into two groups of intervention and control based on a randomized block design. Each patient in the experimental group received one tablet of 400 mg GC supplement and those in the control group received the same amount of placebo (starch) daily for 6 weeks.

Sample size

The sample size in this study, based on the changes in interleukin (IL)-6 levels [35], was calculated as 16 subjects in each group. Considering 30 percent dropouts, a total of about 44 participants were included in this study.

Anthropometric, physical activity, and dietary intake

At the beginning and at the end of the study, the International Physical Activity Questionnaire was employed to evaluate the physical activity of patients. Dietary intake was assessed using a food records questionnaire (including two weekdays and one weekend) at baseline and at the end of week 6. Height and weight were recorded with an accuracy of 0.1 cm and 0.1 kg, respectively. The BMI was calculated for each patient at the beginning, and the end of the study by the formula where kg is a person's weight in kilograms and m² is their height in meters squared (kg/m²). After measuring waist and hip circumference by a meter with 0.1 cm accuracy, the waist-to-hip ratio (WHR) was calculated by dividing these two values.

Assessment of appetite

The short form of the Council of Nutrition Appetite Questionnaire (CNAQ) is called the Simplified Nutritional Appetite Questionnaire (SNAQ). The validation analysis of the questionnaires revealed that the SNAQ is more advised for clinical application due to its briefness and reliability. Four items make up the SNAQ, which are arranged in a single domain.



Each question offers five possible responses, denoted by the letters A through E. According to the following scale, the questions are punctuated: A = 1, B = 2, C = 3, D = 4, and E = 5. They add up to the questionnaire's overall score, which can be anywhere between 4 and 20 [36].

Blood sampling and biochemical measures

At the beginning of the study, before and after the intervention, 7 cc of blood samples were taken after 12 hours of fasting. Sera were isolated by centrifugation (at 3,000 rpm for 5 minutes) until assay at a temperature of –70°C. IL-6, IL-10 and insulin levels were measured by ELISA Kits (Shanghai Crystal Day Biotech Co., Ltd., Shanghai, China) [35]. FBS and components of lipid profiles (triglyceride [TG], Chol, low-density lipoprotein [LDL], and HDL) were measured using specific enzymatic kits (Pars Azmoon, Tehran, Iran) and compared before and after the intervention. HOMA-IR index was measured by this equation: fasting glucose (mmol/L) × fasting insulin (μIU/mL)/22.5 [37].

Statistical analysis

In this study, data were analyzed using SPSS software (version 21; SPSS Inc, Chicago, IL, USA). Quantitative data are reported as mean ± standard deviation (SD), and qualitative data are presented as frequency and percent. The Kolmogorov-Smirnov test was applied to assess the normality of data. Analysis of covariance (ANCOVA) was used to identify differences between two groups after adjusting for confounding variables (age and BMI). To examine differences within each group at baseline and after six weeks, paired t-tests were used. An Independent t-test was used to compare the two groups at the beginning of the study. In this study, p value less than 0.05 was considered significant.

RESULTS

After six weeks of GC / placebo supplementation, 34 patients out of 44 completed the study, and the following results were obtained (**Figure 1**).

Comparison of the demographic characteristics

Table 1 shows the distribution of qualitative and quantitative variables, including education, occupational status, age, and duration of disease. Seventy percent of those in the intervention group and 64 percent in the control group had a university degree. Moreover, 29 percent of subjects in the GC group and 35 percent in control group were housewives. The mean age of the women was 27 (± 5.22) years. The duration of illness in those with GC consumption was six years and in the control group was eight years. There was no significant difference in none of these factors between the two study groups.

Effect of GC on glycemic indices

An Independent t-test was used to compare the mean fasting glucose level, blood insulin level, and insulin resistance in the two groups. In the GC and control groups, the mean at baseline was compared to the mean at week 6, which shows a significant increase in FBS (p = 0.01 and p < 0.001). According to the ANCOVA tests, fasting glucose, insulin levels, and insulin resistance at baseline were not significantly different between the placebo and treatment groups (**Table 2**).





Figure 1. Flow chart of sampling.

Variables	Green coffee (n = 17)	Placebo (n = 17)	p value
Educational status			0.49*
Elementary	1 (5.9)	0 (0)	
Diploma	4 (23.5)	6 (35.3)	
Educational	12 (70.6)	11 (64.7)	
Job status			0.89*
Housewife	5 (29.4)	6 (35.3)	
Employer	5 (29.4)	4 (23.5)	
Student	6 (35.3)	5 (29.4)	
Specialist	1 (5.9)	2 (11.8)	
Age (yr)	27 ± 4.82	27.88 ± 5.71	0.63†
Duration of illness (yr)	6.12 ± 4.34	8 ± 5.50	0.27†

Table 1. Constal sharestoristics of study subject by polycyctic overy syndrome phonetype

Values are presented as number (%) or mean \pm SD.

*p-values are reported based on χ^2 test; †p values are reported based on the analysis of independent sample t-test.

Effect of GC on lipid profile

The levels of lipid biomarkers are shown in Table 3 for both groups before and after the intervention. There was no significant difference between the two groups or in either group before and after the supplement therapy in terms of LDL and HDL. However, the reduced concentrations of TG and cholesterol for GC intervention group were different, compared to those for placebo group (p < 0.05).

Effect of GC on inflammatory biomarkers

In the sixth week ANCOVA test was used to compare the mean levels of IL-6 and IL-10, which did not show a significant difference between the two groups. In the GC and placebo groups, the mean level at baseline was compared to the mean at week 6, which showed no significant difference (Table 4).



Table 2. FBS and insulin levels, HOMA-IR status before and after green coffee intervention in both treatment and
placebo groups

Variables	Green coffee (n = 17)	Placebo (n = 17)	p value*
FBS			
Baseline	103.2 ± 19	98 ± 6	0.28
After	111.8 ± 22	107 ± 6.9	0.35
Difference	8.58 ± 12.75	8.64 ± 5.7	0.91
p value†	0.01	< 0.001	
Insulin			
Baseline	11.43 ± 14.7	8.6 ± 10.64	0.85
After	11.54 ± 14.1	11.88 ± 9.5	0.93
Difference	0.1 ± 6.1	1.24 ± 5.6	0.60
p value†	0.94	0.37	
HOMA-IR			
Baseline	54.32 ± 71.37	47.18 ± 39.57	0.72
After	62.50 ± 79.97	57.92 ± 50.03	0.84
Difference	8.17 ± 38.59	10.73 ± 29.79	0.83
p value†	0.39	0.15	

Values are presented as mean \pm SD.

FBS, fasting blood glucose; HOMA-IR, homeostatic model assessment of insulin resistance; BMI, body mass index. *p values based on analysis of covariance after adjustment for age and BMI; †p values based on paired t-test.

Table 3. Cholesterol, triglyceride, LDL and HDL serum levels before and after green coffee intervention in both
treatment and placebo groups

Variables	Green coffee (n = 17)	Placebo (n = 17)	p value*
тс			
Baseline	196.6 ± 28	178 ± 33	0.08
After	177.7 ± 28.8	190.1 ± 32	0.21
Difference	-18.8 ± 31.26	12.7 ± 31.55	0.03
p value†	0.02	0.11	
TG			
Baseline	104.5 ± 32.7	93.9 ± 61.3	0.53
After	98.5 ± 37.3	128.1 ± 81.7	0.18
Difference	-6.05 ± 34.14	34.23 ± 45.19	0.007
p value†	0.47	0.007	
LDL			
Baseline	97.5 ± 20.5	85.7 ± 23	0.12
After	88.3 ± 15.3	87.5 ± 20.5	0.89
Difference	-9.17 ± 16.85	1.76 ± 21.35	0.40
p value†	0.03	0.73	
HDL			
Baseline	53.5 ± 11	55 ± 11.3	0.68
After	52.8 ± 8.6	55.7 ± 12	0.43
Difference	-0.64 ± 8.69	0.64 ± 7.24	0.48
p value†	0.78	0.71	

LDL, low-density lipoprotein; HDL, high-density lipoprotein; TC, total cholesterol; TG, triglyceride.

*p values based on analysis of covariance after adjustment for age and body mass index; *p values based on paired t-test.

Effect of GC on anthropometric indices

The mean and standard deviation of BMI, waist circumference, hip circumference, WHR, and their changes in the two study groups are reported in Table 5. BMI and waist circumference were slightly reduced in both placebo and treatment groups, which was not significant. The hips at the beginning and end of the study are almost identical. The results of covariance analysis also showed no significant difference between the two groups before and after the study. Also, the WHR increased slightly at the end of the study in the control group, whereas in the treatment group, it decreased minimally (p > 0.05).



Table 4. Serum levels of inflammatory biomarkers before and after green coffee intervention in both treatment and placebo groups

Variables	Green coffee (n = 17)	Placebo (n = 17)	p value*
IL-6			
Baseline	190.8 ± 142.7	166.3 ± 105.1	0.57
After	204.8 ± 168.5	177.7 ± 112.2	0.58
Difference	14.02 ± 57	11.39 ± 44.5	0.83
p value†	0.32	0.30	
IL-10			
Baseline	205 ± 257.3	165.4 ± 169.7	0.52
After	203.5 ± 249.7	171.7 ± 220.6	0.69
Difference	-1.55 ± 20.22	15.27 ± 67.51	0.18
p value†	0.75	0.36	

IL, interleukin.

*p values based on analysis of covariance after adjustment for age and body mass index; †p values based on paired t-test.

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Variables	Green coffee (n = 17)	Placebo (n = 17)	p value*
BMI (kg/m ²)			
Baseline	25.9 ± 6.8	23.74 ± 3.7	0.24
After	25.7 ± 7.1	23.70 ± 3.7	0.29
Difference	-0.2 ± 1.4	-0.04 ± 0.44	0.62
p value†	0.55	0.72	
Waist (cm)			
Baseline	84.1 ± 14.8	84.1 ± 13.9	0.99
After	83.9 ± 13.9	84.9 ± 12.8	0.84
Difference	-0.2 ± 1.6	0.8 ± 2	0.07
p value [†]	0.66	0.12	
Hip (cm)			
Baseline	103 ± 8.7	102.6 ± 9.3	0.91
After	102.9 ± 8.2	102.7 ± 9.5	0.93
Difference	-0.1 ± 1.4	0.1 ± 1.6	0.84
p value†	0.8	0.9	
Waist/hip			
Baseline	0.809 ± 0.084	0.81 ± 0.083	0.86
After	0.81 ± 0.083	0.73 ± 0.28	0.29
Difference	0.0004 ± 0.013	-0.08 ± 0.26	0.21
p value†	0.9	0.21	

BMI, body mass index.

*p values based on analysis of covariance after adjustment for age and BMI; [†]p values based on paired t-test.

Table 6. Appetite score before and after green coffee intervention in both treatment and placebo groups			
Variables	Green coffee (n = 17)	Placebo (n = 17)	p value*
Appetite score			
Baseline	13.3 ± 2.5	13.5 ± 1.7	0.81
After	13.5 ± 2.4	13.7 ± 1.8	0.81
Difference	0.2 ± 0.9	0.2 ± 0.6	0.27
p value†	0.30	0.16	

*p values based on analysis of covariance after adjustment for age and body mass index; †p values based on paired t-test.

Effect of GC on appetite

There was no significant effect of GC on appetite between supplement and placebo groups (**Table 6**).



DISCUSSION

Present study was a double-blind, randomized clinical trial with 34 participants, and those in the intervention group received GC for 6 weeks. The main finding of this study was the hypo-triglyceridemic and hypo-cholesterolemia effects of GC due to its bioactive components.

This study showed no significant change in glycemic indices between groups after the treatment. In line with our findings, Kondo et al. found that drinking caffeinated or decaffeinated coffee had no influence on FBS or insulin levels [38]. In contrast with our findings, Morvaridi et al. [39] have reported that drinking GC has a positive impact on adults' glycemic indices and cardio-metabolic risk factors. In addition, findings from several studies have identified the anti-diabetic effect of CGA. For example, consuming 3–4 cups of high-content of CGA decaffeinated coffee daily can significantly decrease the risk of DM2.

Moreover, CGA has a similar therapeutic effect to metformin and insulin sensitizer properties [40]. Several publications have appeared in recent years documenting the alpha-glycosidase inhibiting activity of CGA in the pancreas in vitro [41,42]. Similarly, there are other studies in rats and humans with the blood glucose lowering effect of CGA or coffee [43]. Another potential biological action of CGA relies on an antagonistic role in the transportation of glucose in the intestine [44]. Based on Welsch et al. study [45], 1 mM CGA is able to reduce the Na+ gradient resulting in attenuated uptake of glucose in an in vitro brush border membrane by approximately 80 percent. In a clinical study by Iwai et al. [46], it was shown that consumption of 100 and 300 mg GC rich in CGA might restrict the activity of an amylolytic enzyme that decreases absorption of intestinal glucose. However, there was no significant difference in insulin levels. Another study by Van Dijk et al. showed some evidence around the putative effect of CGA on reducing glucose and insulin responses justifying the contribution between coffee and low risk of DM2 development [43]. Tunnicliffe et al. [47] studied CGA treatment in rats, resulting in low blood glucose response and some alterations in GIP hormone concentrations. A study by Ong et al. [48] illustrated that CGA could stimulate glucose transport to skeletal muscle through the activation of the AMPK passway for the first time. These results are some evidence around CGA that explain the probable effect of coffee against DM2 [48]. The observed dispute in this regard could be attributed to the use of various types of coffee, duration of study, and dose of the supplement in previous researches.

PCOS, as a heterogeneous clinical syndrome, can affect lipid profile. Dyslipidemia is one of its clinical features with 70 percent prevalence and can increase the risk of DM2 and metabolic syndrome [49,50]. As the current study presents, GC could decrease triglyceride and cholesterol levels without changes in HDL and LDL. In line with our findings, Zuñiga et al. [51] showed that GC and its CGA have hypolipidemic effects on serum levels of TG and TC in patients with impaired glucose tolerance. Further, Shahmohammadi et al. [52] indicated that GC bean extract supplementation (1 g/day) significantly improved TG and TC serum levels after eight weeks of intervention. Since CGA is a phenolic acid with a high concentration in GC beans, it modulates liver metabolic functions such as TG metabolism [53]. One suggested mechanism is through the regulation of peroxisome proliferator-activated receptors (PPARs). These nuclear receptors have the potential to regulate the synthesis, transport, and oxidation of fatty acids. PPAR- α is one of these receptors that has insulin sensitivity and lipid-lowering effect [54]. In an animal study by Wan et al. [55] rats received a high-cholesterol effect from CGA due to the upregulation of PPAR- α and



elevation of fatty acid utilization. Another study by de Sotillo and Hadley [56] showed a significant reduction in fasting plasma concentrations of cholesterol and TG in rats in the dose of 5 mg/kg body weight/day CGA for three weeks, respectively.

In this study, we also evaluated the effect of GC on IL-6 and IL-10; there was no significant change between the two groups. In agreement with our results, in the study by Song et al. [57] a significant reduction in plasma level of IL-6 was observed in mice fed 0.3% GC (300 mg GC extract/kg diet), compared to the high-fat diet (HFD) fed group after 11 weeks. This substantial effect on IL-6 may be caused by the fact that the GCE dose utilized in this investigation for mice was higher than the GCE dose used in our study at 1,460 mg/60 kg. Furthermore, in a study conducted by Hwang et al. [58], mice were injected three times with lipopolysaccharide with or without 0.1 mg CGA (5 mg/kg) for three days, and CGA was found to reduce IL-6 mRNA levels dose-dependently by downregulating nuclear factor κ B (NF- κ B). According to Wu et al. [59] research's giving ApoE-/- mice 400 mg/kg CGA for 12 hours reduced the serum levels of IL-6 compared to the control group. However, in one investigation, high dose CGA infusion (7 mg/kg) for seven days led to an increase in IL-6 and tumor necrosis factor(TNF)- α levels in rats compared to the control group; a low dose (0.3 mg/kg) had no remarkable impact on these biomarkers [60].

Another study by Shin et al. [61] examined the anti-inflammatory role of CGA on the production of IL-8 in the colitis model in C57BL/6 mice, and the results showed the suppression of IL-1 β and macrophage inflammatory protein mRNA expression. These findings suggested that dietary CGA supplementation may relieve intestinal inflammatory conditions. Moreover, Shi et al. [62] showed that CGA supplementation in rat model can modulate liver fibrosis and inflammation through inhibition of some pathways such as toll-like receptor 4 signaling and NF- κ B activation, serum levels of TNF- α and mRNA expression of IL-1 β and IL-6.

Although there is some evidence around the weight management role of GC, the results of our study did not show any significant improvement in BMI and WHR. In line with our findings, Li et al. [63] in an animal study, showed that 0.5% (w/w) GC plus HFD could not reduce weight after 12 weeks. However, in contrast with our result, a clinical trial conducted by Thom [64] on overweight subjects. They showed a significant reduction in weight after 12 weeks of supplementation with GC (11 g/day). Further, an animal study on HFD-induced obese mice with 100 or 200 mg/kg GC for four weeks plus HFD significantly decreased weight and body fat [65]. It has been attributed to caffeine as a major bioactive component of GC that is linked with weight reduction. Moreover, CGA may have the ability to reduce calorie input by inhibiting amylase concentration and glucose absorption [66]. Roshan et al. [28] showed that GC consumption has the ability to control appetite. Furthermore, Bobillo et al. [67] indicated that combining GC with Garcinia C Cambogia and L-carnitine can reduce hunger sensations. The discrepancy between the current study and earlier research could be attributed to a variety of factors, including differences in study designs, methodologies, GCE supplement dosage, and populations.

The results of the current study showed that GC supplement improves lipid profile in women with PCOS even though there was not any improvement in anthropometric measurements, glycemic indices, and inflammatory biomarkers. However, long term studies with different doses are needed to evaluate the anti-inflammatory and hypoglycemic effects of the CGA in PCOs women.



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