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Effects of decaffeinated green coffee extract supplementation on anthropometric indices, blood glucose, leptin, adiponectin and neuropeptide Y (NPY) in breast cancer survivors: a randomized clinical trial

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Objective: This study aimed to evaluate the effects of decaffeinated green coffee extract (DGCE) supplementation on anthropometric indices, blood glucose, leptin, adiponectin, and neuropeptide Y (NPY) in breast cancer survivors with obesity. *Method*: A total of 44 breast cancer survivors with obesity aged between 18 and 70 years and with a mean body mass index (BMI) of 31.62 ± 4.97 kg m^{-2} participated in this double-blind randomized clinical trial. Eligible patients were randomized to the intervention (n = 22) and control (n = 22) groups. They received two 400 mg capsules of DGCE or two identical placebos daily for 12 weeks. Serum concentrations of leptin, adiponectin, NPY, fasting blood sugar, insulin, and homeostatic model assessment for insulin resistance (HOMA-IR) were measured at the baseline and after completion of the intervention. Also, weight, waist circumference, fat percentage, muscle percentage, and visceral fat were measured. *Results*: There were no significant differences in terms of changes of anthropometric indices and concentrations of leptin, adiponectin, NPY, and blood sugar between the two studied groups. *Conclusion*: Supplementation with DGCE in breast cancer survivors with obesity had no significant effect on anthropometric indices and blood glucose, leptin, adiponectin, and NPY levels.

Introduction

Breast cancer (BC) is the most common malignancy and the second leading cause of cancer death in women worldwide, accounting for about 23% of newly diagnosed cancers and 14% of cancer-related deaths in women.[1] Despite improvements in screening and advances in treatment that have reduced breast cancer mortality, the number of women with breast cancer is still increasing.[1]

The etiology of BC is related to both hereditary and environmental factors. Environmental factors include hormone therapy, reproductive factors, alcohol consumption, physical inactivity, and obesity. The latter has been postulated to significantly increase the risk for BC.[2] Several studies have shown that obesity is associated with an increased risk of more aggressive BC and a reduced chance of survival.[3,4] Weight gain is one of the known consequences of adjuvant therapies for breast cancer, whereby about 50 to 90% of women experience significant weight gain during treatment, and many who maintain their weight during treatment may also experience progressive weight gain in the following months and years.[1] Therefore, obesity can be considered a common problem in breast cancer survivors, and can increase the risk of cancer mortality and recurrence.[5]

Obesity can increase the risk of BC recurrence by several mechanisms such as increased estrogen levels due to overactive adipose tissue, insulin resistance, excessive secretion of the insulin-like growth factor (IGF), increased oxidative stress,

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hypercholesterolemia, and production of adipokines which are secreted by fat cells.

The two most important adipokines secreted by the adipose tissue are leptin and adiponectin.[6] It has been suggested that leptin reduces food intake, weight, and body fat by affecting the satiety centers in the hypothalamus. Adiponectin increases insulin sensitivity and is inversely related to BMI and waist circumference.

It has been reported that in individuals with obesity, leptin levels increase and adiponectin levels decrease, which may lead to insulin resistance[6] and consequently cancer progression risk.[7] In contrast, weight loss reduces leptin levels, increases adiponectin, and improves insulin resistance.[6]

NPY is a hormone that is secreted by the hypothalamus and peripheral adipose tissue. Excessive NPY secretion can stimulate appetite, overeating, and excessive energy intake, which can lead to obesity and an increased risk of diabetes, heart diseases, and other chronic diseases.[8] Several studies have shown that NPY is involved in a number of mechanisms involved in cancer progression, including cell proliferation, angiogenesis, and metastasis, especially in neuroblastoma, and breast and prostate cancer.[8]

Due to the consequences of obesity, various strategies have been used to control weight in BC patients and several dietary supplements have been studied in this regard. Coffee is one of the most consumed beverages in the world.[9] Green coffee beans are rich in chlorogenic acid (CGA) and related compounds such as quinic acid, *p*-coumaric acid, and caffeic acid. The compounds are similar in green and roasted coffee; however, some of these compounds are lost during the roasting process. Moreover, hydroxy-hydroquinine which is produced during the roasting process affects the performance of chlorogenic acid.[10] Green coffee bean extract (GCE) inhibits glucose 6 phosphatase through CGA, and therefore can reduce the release of glucose through glycogenolysis and thus can cause more utilization of lipids as an energy source.[11] It can also improve lipolytic activity by altering metabolic pathways and decreasing fat absorption by inhibiting pancreatic lipase.[12]

Several studies have shown that green coffee bean extract and chlorogenic acid can be effective in controlling weight and appetite and improving insulin resistance.[13–15] Some studies have shown that supplementation with green coffee extract can reduce leptin and increase adiponectin levels.[16–18] In addition to the evidence for its protective effect against obesity, GCE has also been reported to exert an anti-tumor activity. Several studies have reported the effects of chlorogenic acid in preventing the beginning, progression, and spread of cancer[19] as well as inhibiting deoxyribonucleic acid (DNA) methylation in human breast cancer cells.[19] Chlorogenic acid has also been shown to exert its antitumor effect by inducing apoptosis in many human cancer cells.[20] To the best of our knowledge, no clinical trial has been conducted previously addressing the effect of DGCE on anthropometric indices, appetite levels, and serum adipokine concentrations in BC survivors. The aim of this clinical trial is to examine the effect of DGCE on anthropometric indices and levels of leptin, NPY, adiponectin, insulin, insulin resistance, and FBS in breast cancer survivors with obesity.

Materials and methods

Participants

Forty-four BC survivor women who met the eligibility criteria were entered into our final analysis. The participants were selected from the patients referred to the Motamed Breast Cancer Research Center in Tehran from April 2019 to February 2020. Inclusion criteria were age between 18 and 70 years, BMI above 25 kg m^{-2}, having recovered from breast cancer and being breast cancer-free for at least six months, and have not received radiotherapy or chemotherapy in the last 3 months.

Exclusion criteria were pregnancy and lactation, adherence to unusual weight loss diets during the three months before the start of the study, consumption of slimming and fat-burning drugs, daily consumption of coffee, allergic reactions, gastrointestinal symptoms such as stomach pain, cancer recurrence and not taking dietary supplements.

Given that the mean difference of interest for adiponectin concentration between the two groups was 4 ng dl^{-1},[16] we required a sample size of 20 patients in each group to obtain an α error of 0.05 and a power of 80% (β = 0.2). As shown in the flow diagram of study participants in Fig. 1, a total of 62 patients were randomly assigned to two groups of 31 individuals consuming DGCE or placebo. During the intervention, nine patients consuming DGCE supplements and nine patients from the placebo group were excluded from the trial because of inadequate compliance with supplementation, breast cancer recurrence, allergic reaction (skin rash), stomach ache, and unwillingness to continue the intervention. Ultimately, data analysis was performed for 44 patients, 22 in the intervention group and 22 in the placebo group, who completed the trial. There was no significant difference between the two groups in terms of dropouts.

Study design and intervention

In this randomized, double-blind, placebo-controlled trial study, women who were referred to the clinic with a history of breast cancer and at least three months passed since their last treatment and met the eligibility criteria were invited to participate in this trial.

First, the procedure of conducting the study was explained to each participant, and if they wished to participate in the study, they were asked to give written consent.

One of the investigators filled out a questionnaire regarding smoking status, current diseases, prescribed medication, and dietary supplementation history by interviewing the participants at the beginning of the study. Bottles containing supplements or placebo were labeled A or B by the manufacturing company. Blinding of participants and investigators was maintained until the end of the statistical analysis. Participants were stratified using the hormonal receptor (HR) and human

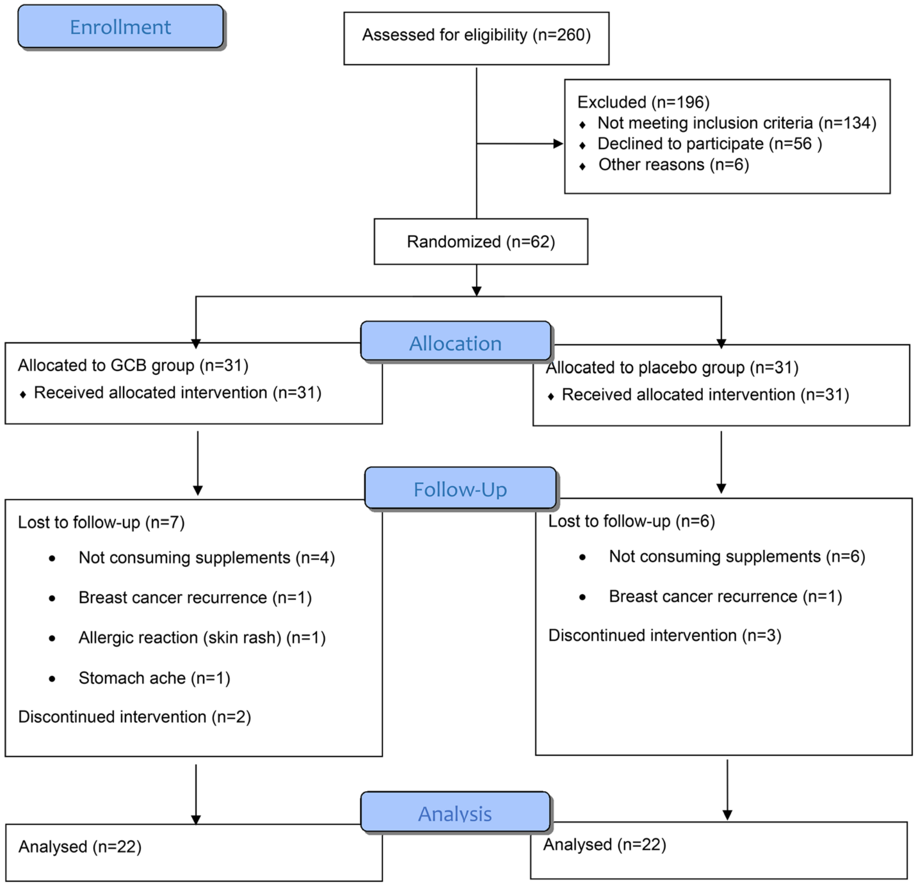

Fig. 1 Flow diagram of the patients during the clinical trial.

epidermal growth factor receptor 2 (HER2) status and were randomly assigned to one of the two groups receiving supplement bottles with code A or B by using the stratified block randomization method. In this method, six blocks of 4 bottels (AABB, ABAB, BABA, BBAA, BAAB, ABBA) were placed in a container, and an investigator allocated the participants to one of the intervention groups. Patients in the green coffee and placebo groups were expected to consume supplements containing 400 mg green coffee extract or identical placebos twice a day, before their main meals, for 12 weeks. Each patient received three supplement bottles containing 70 capsules (sufficient for 35 days) at the beginning of the study and in the fourth and eighth weeks of the trial. To assess patients' compliance with the supplementation, they were followed up through phone calls every seven days. The researcher counted the remnant capsules in the returned supplement bottles at each follow-up visit. Breast cancer survivors took tamoxifen in the premenopausal stage and letrozole in the postmenopausal stage according to their estrogen and progesterone receptor status, and these drugs have no specific nutritional side effects. Furthermore, it has been found that chlorogenic acid in green coffee abates the toxicity of tamoxifen in animal studies.[21,22]

Subjects were instructed to avoid changing their physical activity during the study and they were followed up weekly through phone calls to ensure the proper regime of supplement or placebo use and to improve the retention rate and decrease dropouts.

Also, to assess adherence, subjects were asked to bring the bottles containing the remainder of the capsules on the second visit in the 6^{th} week of the trial. In case the subject had consumed less than 90% of the capsules, she was excluded from the trial.

The primary outcomes of this study were the changes in anthropometric indices and levels of leptin, NPY, adiponectin, insulin, insulin resistance, and FBS, and the secondary outcomes were changes in dietary intake and physical activity of participants.

This study was approved by the ethics committee of the National Nutrition and Food Technology Research Institute of Shahid Beheshti University of Medical Sciences (IR.SBMU.nnftri.Rec.1397.219) and registered at ClinicalTrials.gov (NCT03394690).

Measurement of anthropometric indices

The height of each subject was measured without shoes, using non-stretch tape (Seca, Hamburg, Germany), and recorded to the nearest 0.5 cm at the baseline. The weight of each patient was measured with light clothing and using a digital scale with a precision of 0.1 kg (Seca, Hamburg, Germany). Also, body fat percentage, body muscle percentage, and visceral fat were measured using Omron company's body composition monitor[23] at the baseline and end of the study. BMI was also calculated by dividing the weight (kg) by the square of the height (m^2). Waist circumference was also measured as the distance between the top of the iliac crest bone and the last rib, approximately in the umbilical region, at the baseline and end of the study with a tape meter with a precision of 0.5 cm.

Measurement of biochemical parameters

Following a 12-hour fasting period, a 5cc arm vein blood sample was taken at the baseline and end of the study. The serum from blood samples was separated using a centrifuge at 4000 rpm for 5 minutes. Then, the serum samples were aliquoted into micro-tubes and were frozen at −80 °C. Serum levels of leptin, NPY, adiponectin, and insulin were assessed using ELISA kits (respectively, DuoSet ELISA kit, R&D Systems; DuoSet ELISA kit, R&D Systems; DuoSet ELISA kit, R&D Systems; and ZellBio GmbH, Ulm, Germany). FBS was measured by using commercial kits (Pars Azmoon).

Dietary intake assessment and physical activity assessment

Assessment of energy intake, carbohydrates, protein, total fat, and fiber was performed using a three-day food record (including two weekdays and one weekend) at the baseline, in the sixth week, and at the end of the intervention.

At each visit, subjects were instructed on how to record each drink or food consumed during the day, for 3 days. The exact amount of food and beverages recorded in the 3-day 24-hour dietary recall was determined through interviews using household scales. Then, the portion sizes of food and beverage consumed were converted to grams and the food record analysis was performed using Nutritionist IV software. Physical activity was evaluated using the metabolic equivalent of task (MET) questionnaire at the beginning and end of the study.[24]

Decaffeinated green coffee extract (DGCE) supplement

DGCE and placebo capsules were obtained from Arjuna Company in India. According to the HPLC results which were provided by the manufacturing company, each DGCE capsule contains 46.45% chlorogenic acid. The ratio of raw material (green coffee beans) to the extract is 6 : 1. This means that each 400 mg capsule of DGCE is equivalent to 186 mg of CGA and 2400 mg of green coffee beans. The total amount of polyphenols in the DGCE is 53.8%.

Chlorogenic acid in these capsules includes 5-caffeoylquinic acid (5-CQA), 3-caffeoylquinic acid (3CQA), 4-caffeoylquinic acid (4CQA), 3,4-dicaffeoylquinic acid, 3,5-dicaffeoylquinic acid, 4,5-dicaffeoylquinic acid, 3-feruloylquinic acid, 4-feruloylquinic acid and 5-feruloylquinic acid. 5CQA and 3CQA were the main components of CGA, accounting for about 35 to 40 percent and 10 to 15 percent of the total CGA content.

In previous studies, it has been observed that taking green coffee extract supplements up to a dose of 1050 mg per day has no side effects.[25] In the present study, two doses of 400 mg day^{-1} DGCE were used.

Statistical analysis

In the present study, data analysis was performed using Statistical Package for the Social Sciences (SPSS) software version 22. First, the normality of the data was assessed by the Kolmogorov–Smirnov test. For quantitative variables, the paired sample *t*-test or Wilcoxon signed-rank test was used to compare the variables before and after the intervention. To compare the changes between the two studied groups, an independent *t*-test or Mann–Whitney *U* tests were applied, and *p*-values less than 0.05 were considered significant.

Results

Baseline characteristics

Table 1 shows the mean ± standard deviation of quantitative variables including age, height, weight, waist circumference, visceral fat, body fat percentage, body muscle percentage, and body mass index at the baseline in the two groups. There was no significant difference in terms of the above-mentioned variables between the two groups.

Dietary intake and physical activity level

The dietary status and physical activity of the participants are shown in Table 2. The mean values of calorie, macronutrient, and micronutrient intake at the baseline were not statistically significant between the two groups. There was no significant difference between the two groups in terms of physical activity at the beginning and end of the study.

Anthropometric measurements

As shown in Table 3, the mean weights were significantly decreased in both intervention and control groups (in the

Table 1 Baseline characteristics of the participants in both study groups

Baseline variables	GCE group (n = 22)	Placebo group (n = 22)	P*
Age (year)^b	52.90 ± 8.77	54.81 ± 8.81	0.42
Height (cm)^a	157.86 ± 6.75	157.63 ± 5.45	0.79
Weight (kg)^b	78.06 ± 12.24	79.26 ± 13.79	0.76
BMI (kg m^{-2})^b	31.41 ± 5.01	31.84 ± 5.04	0.77
WC (cm)^b	104.25 ± 11.54	106.27 ± 11.34	0.56
Body fat (%)^a	41.28 ± 5.39	43.3 ± 5.17	0.21
Muscle mass (%)^a	26.03 ± 2.56	24.81 ± 2.21	0.1
Visceral fat^b	10.27 ± 2.47	10.68 ± 2.74	0.6
Smoking status, n (%)^c			
Yes	1 (4.54%)	0 (0%)	0.30
No	21 (95.46%)	23 (100%)	

GCE, green coffee extract; WC, waist circumference. *P values are for comparison of the baseline variables between the two groups. ^{a} Data are expressed as mean ± standard deviation and tested by the independent sample t-test. ^{b} Data are expressed as mean ± standard deviation and tested by the Mann–Whitney U test. ^{c} Data are tested by the chi-square test.

Table 2 Dietary intake and physical activity of the participants during the intervention

	DGCE group (n = 22)			Placebo group (n = 22)					
	Baseline Mean ± SD	Week 6 Mean ± SD	Week 12 Mean ± SD	Baseline Mean ± SD	Week 6 Mean ± SD	Week 12 Mean ± SD	P*	P†	P‡
Energy (kcal d^{-1})	1832.6 ± 308.7	1699.8 ± 248.6	1606.9 ± 231.8	1744.6 ± 259.7	1723.5 ± 232.7	1679.4 ± 243.3	0.31^a	0.75^a	0.71^a
Carbohydrate (g d^{-1})	191.4 ± 55.6	164.4 ± 40.2	171.5 ± 42.2	183.4 ± 43.18	175.5 ± 40.4	161.7 ± 54.3	0.6^a	0.38^a	0.52^a
Protein (g d^{-1})	57.5 ± 13.6	52.4 ± 15.9	56.1 ± 12.8	52.8 ± 10.15	54.1 ± 16.26	52.2 ± 12.99	0.2^a	0.73^a	0.34^a
Fat (g d^{-1})	39.3 ± 13.8	38.5 ± 10.1	34.6 ± 9.0	35.3 ± 12.5	35.5 ± 12.15	37.5 ± 10.65	0.33^a	0.38^a	0.34^a
Fiber (g d^{-1})	13.3 ± 5.6	11.5 ± 4.9	12.3 ± 4.7	13.41 ± 3.7	12.1 ± 3.5	10.39 ± 3.9	0.94^a	0.61^a	0.15^a
Calcium (mg d^{-1})	596.0 ± 266.6	497.9 ± 335.1	486.2 ± 284.3	520.39 ± 211.8	528.3 ± 220.3	484.8 ± 223	0.31^a	0.73^a	0.98^a
Magnesium (mg d^{-1})	200.1 ± 115.0	154.5 ± 68.8	166.9 ± 55.9	155.4 ± 38.7	154.03 ± 40.8	141.1 ± 33.8	0.09^a	0.97^a	0.08^a
Selenium (mg d^{-1})	0.07 ± 0.02	0.05 ± 0.03	0.06 ± 0.02	0.05 ± 0.02	0.06 ± 0.02	0.06 ± 0.02	0.11^a	0.22^a	0.88^a
Zinc (mg d^{-1})	6.2 ± 2.2	5.7 ± 1.8	6.0 ± 1.5	5.7 ± 1.6	5.8 ± 2.03	5.5 ± 1.3	0.42^a	0.81^a	0.35^a
Vitamin C (mg d^{-1})	128.6 ± 73.6	93.4 ± 58.1	92.3 ± 56.3	126.6 ± 48.3	96.7 ± 46.8	84.1 ± 54.4	0.91^a	0.83^a	0.63^a
Vitamin E (mg d^{-1})	4.6 ± 4.3	3.6 ± 4.5	2.5 ± 1.6	2.5 ± 1.4	3.2 ± 3.6	3.5 ± 3.5	0.11^b	0.89^b	0.4^b
Physical activity (MET·h d^{-1})	37.4 ± 3.4	—	36.8 ± 3.1	39.2 ± 5.8	—	38.5 ± 5.1	0.22^a	—	0.20^a

DGCE, decaffeinated green coffee extract; MET, metabolic equivalent of the task; SD, standard deviation. *P values are for comparison between the two groups at the baseline. †P values are for comparison between the two groups after 6 weeks. ‡P values are for comparison between the two groups after 12 weeks. ^{a}P values were obtained from the independent sample t-test. ^{b}P values were obtained from the Mann–Whitney U test.

DGCE group p = 0.008 and in the placebo group p = 0.005). However, the mean weight changes were not significantly different between the two groups at the end of the intervention period.

In addition, the mean waist circumference, body fat percentage, and visceral fat also decreased significantly in both groups at the end of the study, but the mean changes of these indices were also not significantly different between the two groups.

The mean percentage of lean body mass in the intervention group decreased significantly; however, this decrease was not significant compared with the placebo group.

Biochemical parameters

According to Table 3, we did not observe any significant difference in the mean changes of adiponectin, leptin, and NPY concentrations in the two groups. Mean insulin and HOMA-IR concentrations in the intervention group significantly decreased at the end of the study compared to the beginning, but this decrease was not significant in comparison with the control group. We also did not observe a significant difference in FBS concentration between the two groups at the end of the study.

Discussion

The present study showed that 12 weeks of supplementation with DGCE (800 mg d^{-1} green coffee extract, 372 mg d^{-1} chlorogenic acid) had no significant effect on anthropometric indices and levels of insulin, insulin resistance, FBS, leptin, adiponectin, and NPY in overweight or obese BC survivors. In the present study, the daily energy intake in both groups decreased at the end of the study compared to the baseline; however, this reduction was not significant. Since we did not prescribe a weight loss diet and the physical activity of the participants did not change during the study, the reduction in calorie intake may be due to decreased appetite during the study. Several mechanisms have been reported for the effect of green coffee on weight loss, including improving lipolytic activity by altering metabolic pathways and reducing fat absorption by inhibiting pancreatic lipase. Song *et al.*[12] suggested that GCE could reduce visceral fat and weight by inhibiting adipogenesis. GCE can also reduce glucose release through glycogenolysis by inhibiting glucose-6-phosphatase, and thereby it can propel the body to use lipids as an energy source.[11] In the present study, no significant differences were observed in weight, BMI, visceral fat, fat percentage, and waist circumference. These results are in accordance with several previous studies. For instance, in a study of 70 people with dyslipidemia after 8 weeks of supplementation with 800 mg d^{-1} DGCE (containing 50% chlorogenic acid), no significant difference was observed between the studied groups in terms of weight and BMI.[26] Similarly, the results of Shahmohammadi *et al.*[27] demonstrated that green coffee supplementation has no effect on appetite and anthropometric indices in patients

Table 3 Dependent variables at the baseline and after the intervention and their changes throughout the trial in both groups

	Baseline Mean ± SD	Week 12 Mean ± SD	Changes Mean ± SD	P*	P†	P‡
Weight (kg)						
DGCE	78.06 ± 12.24	77.12 ± 12.25	−0.94 ± 1.50	0.008[b]	0.783[c]	0.815[c]
Placebo	79.26 ± 13.79	78.2 ± 13.76	−1.05 ± 1.56	0.005[b]		
BMI (kg m^{-2})						
GCE	31.41 ± 5.01	31.02 ± 4.95	−0.38 ± 0.62	0.009[b]	0.792[c]	0.874[c]
Placebo	31.84 ± 5.04	31.43 ± 5.1	−0.41 ± 0.6	0.004[b]		
WC (cm)						
GCE	104.25 ± 11.54	102.59 ± 11.70	−1.65 ± 3.70	0.04[b]	0.705[c]	0.423[d]
Placebo	106.27 ± 11.34	103.88 ± 10.79	−2.38 ± 2.88	0.001[b]		
Body fat (%)						
GCE	41.28 ± 5.39	39.83 ± 5.38	−1.45 ± 2.79	0.024[a]	0.154[c]	0.635[c]
Placebo	43.3 ± 5.17	42.18 ± 5.37	−1.11 ± 1.82	0.009[a]		
Muscle mass (%)						
GCE	26.03 ± 2.56	26.65 ± 2.64	0.61 ± 1.37	0.047[a]	0.051[c]	0.452[c]
Placebo	24.81 ± 2.21	25.14 ± 2.31	0.32 ± 1.16	0.201[a]		
Visceral fat						
GCE	10.27 ± 2.47	9.68 ± 2.05	−0.59 ± 1.14	0.024[b]	0.542[c]	0.819[d]
Placebo	10.68 ± 2.74	10.0 ± 1.86	−0.63 ± 1.46	0.05[b]		
Leptin (ng ml^{-1})						
GCE	2491.1 ± 485.7	2549.3 ± 325.5	58.12 ± 420.5	0.524[b]	0.936[c]	0.408[d]
Placebo	2584.8 ± 353.1	2558.5 ± 422.5	−26.3 ± 218.5	0.578[b]		
Adiponectin (pg ml^{-1})						
GCE	18.43 ± 16.95	15.98± 15.9	−2.44 ± 14.1	0.426[b]	0.453[d]	0.312[d]
Placebo	12.41 ± 14.25	13.86 ± 17.02	1.4 ± 10.9	0.541[b]		
NPY (mg l^{-1})						
GCE	1317.96 ± 473.7	1310.12± 496.5	−7.8 ± 143.4	0.81[b]	0.104[c]	0.14[c]
Placebo	1228.4 ± 466.4	1140.2 ± 314.3	−88.2 ± 195.2	0.04[b]		
Insulin (mg l^{-1})						
GCE	16.01 ± 10.8	12.6 ± 7.7	3.3 ± 5.1	0.006[b]	0.374[c]	0.226[d]
Placebo	11.9± 7.6	10.3 ± 9.2	1.5 ± 4.3	0.1[b]		
Insulin resistance						
GCE	5.16 ± 3.54	4 ± 2.99	−1.15 ± 1.77	0.006[b]	0.264[c]	0.162[d]
Placebo	3.48 ± 2.47	3 ± 2.87	−0.47 ± 1.35	0.11[b]		
FBS						
GCE	133.7 ± 41.27	129.5 ± 36.2	−4.2 ± 15.03	0.202[b]	0.065[d]	0.556[b]
Placebo	116.07 ± 31.9	114.02 ± 33.13	−2.04 ± 8.2	0.26[b]		

GCE, green coffee extract; BMI, body mass index; WC, waist circumference; NPY, neuropeptide Y; SD, standard deviation. *P values are for comparison of variables at the baseline and after the trial within each group. †P values are for the comparison of variables between the two groups after 12 weeks. ‡P values are for comparison of changes in variables during the intervention between the two groups. [a]P values obtained from the paired sample t-test. [b]P values obtained from the Wilcoxon signed-rank test. [c]P values obtained from the independent sample t-test. [d]P values obtained from the Mann–Whitney U test.

with non-alcoholic fatty liver disease (NAFLD). The duration of this intervention was 8 weeks and the dose of chlorogenic acid used was 1 g day^{-1}. Furthermore, Mansour *et al.*[28] reported that 6 months of supplementation with 200 mg day^{-1} chlorogenic acid alone and with caffeine had no significant effect on the weight of diabetic patients with NAFLD. In the study of Watanabe *et al.*,[29] 140 mg d^{-1} chlorogenic acid for 12 weeks in patients with hypertension did not cause significant weight loss. Another study in 2011 reported that consumption of caffeinated coffee (containing 345 mg d^{-1} caffeine and 302 mg d^{-1} chlorogenic acid) and decaffeinated coffee (containing 216 mg d^{-1} chlorogenic acid) for 8 weeks had no significant effect on weight and BMI in overweight people.[30] Furthermore in an experimental study, consumption of chlorogenic acid with a high-fat diet for 12 weeks did not cause significant weight loss in mice.[31] In contrast, other studies showed that the use of green coffee caused significant weight loss in the study population. In a clinical trial by Hosseinabadi *et al.*,[32] supplementation with 800 mg d^{-1} green coffee extract in 48 NAFLD patients caused 1.64 kg weight loss after 8 weeks in the intervention group. It has been reported by Martínez-López *et al.*[33] that in 52 healthy and hypercholesterolemic individuals, 8 weeks of consumption of green/roasted coffee, 6 g day^{-1} (445 mg caffeoylquinic acid and 121 mg caffeine), could cause 0.5 to 1 kg weight loss in comparison with the control group. In a study conducted in 2019[34] among 142 overweight people, it was found that daily consumption of 369 mg chlorogenic acid (intervention group) compared to 35 mg chlorogenic acid (control group) caused only 100 g weight loss after 12 weeks and decreased visceral fat and waist circumference, which was significant compared to the controls. According to the results of the aforementioned studies, although some found a statistically significant weight reduction, this weight loss was not probably clinically significant.

It could be argued that studies that have reported clinically significant weight loss due to green coffee have used an energy-restricted diet in addition to green coffee supplementation. For example, Dellalibera *et al.*[35] observed a significant reduction in weight, BMI, and body fat percentage by using a weight-loss diet with 400 mg of DGCE per day for 60 days. In another study, Haidari *et al.*[16] evaluated the effect of energy restriction along with supplementation with green coffee extract on body composition. The results showed a significant reduction in weight, BMI, fat mass, and waist-to-hip ratio after 8 weeks. In this study, no significant change was observed in visceral fat. In addition, in a clinical trial of 34 patients, it was shown that a dose of 800 mg GCE per day, along with diet and weight loss recommendations, significantly reduced waist circumference, but the reductions of weight and BMI were marginally significant.[36] In these studies, although the duration of the intervention and the dose of GCE used were less than in our study, the anthropometric indices decreased significantly, which could be due to the application of energy restriction along with green coffee supplementation. Moreover, due to the synergistic effect of caffeine and chlorogenic acid, caffeinated green coffee extract is better than caffeine alone or chlorogenic acid alone in inhibiting weight gain.[37,38] Because caffeine can produce more heat in the body and chlorogenic acid can reduce glucose uptake and the activity of sterol regulatory element-binding protein (SREBP), a combination of these two compounds may have a synergistic effect to prevent lipogenesis.[39]

In the present study, DGCE supplementation could significantly reduce insulin and HOMA-IR levels in the intervention group compared with the baseline; however, this decrease was not significant in comparison with the control group. It has been proposed that CGA delays intestinal glucose uptake by inhibiting glucose-6-phosphatase translocase-1 and reducing sodium-based glucose transport.[40] CGA and its derivatives appear to reduce hepatic glucose output by inhibiting glucose 6-phosphatase activity.[41,42] In addition, some studies have reported an inhibitory effect of CGA on α-amylase activity (a key enzyme for digestion of dietary carbohydrates). Therefore, inhibition of α-amylase can be a useful strategy for controlling blood sugar by reducing glucose uptake.[43,44] The effect of low-dose green coffee supplementation has been investigated in several studies.[45–47] Studies that examined the effect of 200 mg day^{-1} green coffee extract in patients with hypertension[45] and type 2 diabetic patients with NAFLD[28] have not shown any improvement in FBS, insulin, and HOMA-IR. In the present study, despite the use of higher doses, no effect was observed on these indicators, and these results are inconsistent with the findings of Roshan *et al.*[36] and Shahmohammadi *et al.*,[27] who observed a significant decrease in FBS and HOMA-IR in patients with metabolic syndrome and NAFLD at the same dose or higher than ours; however, similar to our results, Ochiai *et al.*[48] by using higher doses (598 mg CGA) did not observe any effect on FBS in healthy individuals. This may be because basal FBS and insulin resistance levels are higher in people with NAFLD and metabolic syndrome than in healthy people. Just as other examples, Heidari *et al.*[16] using a dose of 400 mg green coffee extract did not observe any significant effect on FBS, insulin, and insulin resistance in healthy obese women, while Hosseinabadi *et al.*[32] using a similar dose and duration showed a significant decrease in FBS and HOMA-IR in NAFLD patients. The use of high doses of chlorogenic acid (1200 mg d^{-1}) in a clinical trial[49] in patients with impaired glucose tolerance (IGT) decreased FBS and insulin and increased insulin sensitivity. In the present study, supplementation with a safe dose of DGCE in people with normal blood sugar did not affect blood sugar.

Also, the results of the present study are consistent with two meta-analyses and a review[50–52] that reported that green coffee extract has no significant effect on insulin and HOMA-IR levels.

In the present study, changes in plasma leptin and adiponectin levels in the two groups were not significant. Some studies have shown that GCE may affect adiponectin gene expression.[53] CGA increases adiponectin levels by inducing peroxisome proliferator-activated receptor gamma (PPAR-γ) transcription activity. In fact, PPAR-γ affects adiponectin by controlling the expression of the adiponectin gene in adipose tissue.[18] It has also been suggested that CGA can exert its anti-diabetic effects through the adiponectin receptor signaling pathway.[54] Eighty percent of leptin is produced by subcutaneous adipose tissue. CGA has been shown to reduce fat mass, which in turn can reduce leptin concentration.[17] The findings of the present study are consistent with the results of some previous ones. Mansour *et al.*[28] showed that 6 months of supplementation with 200 mg d^{-1} chlorogenic acid alone or with caffeine did not cause significant changes in adiponectin levels. In the study by Wedick *et al.*,[30] it was shown that 8 weeks of caffeinated coffee consumption (containing 345 mg of caffeine and 302 mg of chlorogenic acid) could significantly increase adiponectin, while decaffeinated coffee (containing 216 mg of chlorogenic acid) could not significantly increase adiponectin levels in overweight people. Other studies have shown that low-caffeine GC supplementation (below 2%) did not significantly alter leptin and adiponectin levels in obese NAFLD patients.[32,55] Another study[38] showed that supplementation with green coffee + caffeine and also supplementation with caffeine alone reduced leptin in mice, while supplementation with green coffee alone did not affect leptin concentration. However, a recent review article reported that the effect of coffee consumption on leptin concentration is still under debate.[56] By comparing these results with the present study, it can be said that the presence of caffeine and its dosage may be an important intervening factor in determining the effect of GCE on the serum levels of adiponectin and leptin and regulating blood sugar.[57]

Heidari *et al.*[16] after 8 weeks of supplementation with 400 mg day^{-1} green coffee extract along with energy restriction observed a significant increase in adiponectin and a decrease in leptin concentration in the intervention group. Maybe energy restriction is also an important factor affecting the concentration of leptin and adiponectin, and perhaps DGCE alone cannot affect the concentration of these adipokines, and therefore its use along with energy restriction makes it more effective. In addition, Madsen *et al.*[58] reported that a weight loss of more than 10% is necessary to cause a significant change in adiponectin concentration in obese people.

To the best of our knowledge, our trial is the first study investigating the DGCE supplementation effect on NPY concentration. Few studies have examined the effect of coffee on NPY. Greenberg and Geliebter[59] showed that decaffeinated coffee consumption can increase peptide YY (PYY), and on the other hand, Batterham *et al.*[60] found evidence that PYY can suppress NPY neurons and thereby reduce appetite. Concerning the present study, NPY levels and food intake were not significantly changed during the study.

The present randomized controlled trial has some strengths and also some limitations. The double-blind randomized, placebo-controlled design and the weekly follow-up of the participants are the strengths of this study.

The limitation of the present study is its small sample size which makes the generalizability of the findings difficult. The budget deficit for conducting more laboratory tests and investigating gene expression was another limitation of the present study.

Conclusion

Overall, the findings of the present study show that DGCE supplementation at a dose of 800 mg per day for 3 months could not significantly affect the serum levels of leptin, adiponectin, and NPY in BC survivors. Moreover, DGCE did not affect blood glucose and anthropometric measurements of obese or overweight BC survivors.

Author contributions

EH and JH conceived the presented idea. MA and EH developed the proposal, obtained ethical approvals, and applied for funding. MA, Z SM, SH, and MB contributed to the implementation of the study. MA, JN, JH, and SH performed the analysis of the data. MA, SR, and EH wrote, reviewed, and edited the first draft. MA, SH, Z SH, MB, and EH supervised and administered the project. All authors reviewed and approved the final version of the manuscript.

Conflicts of interest

The authors declare no conflicts of interest.

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