Original Article

The Therapeutic Impact of Garlic (Allium Sativum) on Oxidative Stress Markers among Polycystic Ovary Syndrome Patients: A Randomized, Double-Blinded Clinical Trial

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Abstract

Background: The present study aimed to investigate the effect of garlic supplementation on oxidative stress markers in patients with polycystic ovary syndrome (PCOS). **Methods:** Eighty patients with PCOS were randomized and instructed to consume either garlic supplementation (800 mg/day) or a placebo (starch) for 8 weeks. They were also asked to avoid intake of any other supplement during the study. Oxidative stress-related markers including total antioxidant capacity, catalase, glutathione, malondialdehyde concentrations, and anthropometric measures were assessed at baseline and end of the trial. **Results:** Garlic supplementation resulted in significant improvement in catalase concentration (1.82 ± 9.28 vs. –1.55 ± 8.66; *P* value: 0.03), glutathione levels (29.15 ± 57.53 vs. 2.42 ± 77.51; *P* value: 0.048) as well as weight (–0.64 ± 1.94 vs. 0.11 ± 0.82; *P* value: 0.04), body mass index (BMI; –0.25 ± 0.75 vs. 0.05 ± 0.61; *P* value: 0.04), and waist circumference (–0.21 ± 0.77 vs. 0.02 ± 0.65; *P* value: 0.01). However, we failed to detect any significant change in hip circumference, waist to hip circumference ratio, total antioxidant capacity, and malondialdehyde levels between the two groups. **Conclusions:** The present study indicates that garlic supplementation could be beneficial in improving oxidative stress and weight loss among PCOS women.

Keywords: *Garlic, oxidative stress, polycystic ovary syndrome*

Introduction

Polycystic ovary syndrome (PCOS) is a common endocrine disorder that affects women of reproductive ages,[1,2] with a global prevalence of 2.2 to 22.5% that varies based on ethnicity and different diagnostic criteria.[3,4] It is characterized by the occurrence of polycystic ovaries concomitant with dysfunction in ovulation and excessive secretion of androgens from the ovaries and/or adrenal glands.[5,6] Not only does PCOS has a negative effect on patients by itself as it can increase the chance of infertility but it also put them at risk for multiple metabolic comorbidities such as type 2 diabetes, glucose intolerance, dyslipidemia, vascular disease, and endometrial carcinoma.[7,8] Lifestyle changes are the first and most important step in the prevention and treatment of PCOS[9]; yet, it has not been enough, as the number of patients is on the increase.[10] In this regard, many investigators are interested in functional foods. Several medicinal plants have been suggested to be a potential remedy for PCOS improvement.[11]

Garlic (*Allium sativum*), belonging to the *Lilliaceae* family, is one of the most frequently used vegetables.[12] It has traditionally been used for medical properties along with seasoning applications for many years.[13] Garlic consists of several bioactive components, such as alliin (S-allyl-l-cysteine sulfoxide), allicin (diallyl thiosulfinate), and γ-glutamyl-l-cysteine peptide,[14,15] which are addressed to be the main causes of garlic therapeutic activity on hypertension, hyperlipidemia, and metabolic syndrome.[16,17] Furthermore, garlic bioactive ingredients such as polyphenol compounds show antioxidant activity and reduce oxidative stress levels; indeed, the antioxidative properties of garlic have been previously shown in different diseases.[18]

Despite what has just been mentioned about the potentially favorable effects of garlic in improving oxidative stress in different

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diseases,[19,20] as a variety of disorders are involved with different casualties, subsequently, they have a different response to a single treatment. Furthermore, an increased oxidative stress level in PCOS has been previously shown, so it could be posited that functional foods with anti-oxidative properties could be beneficial for the syndrome. In this regard, the present study was performed to investigate the effects of garlic supplementation on oxidative stress levels.

Methods

Participants

The present study was a double-blinded randomized control trial conducted on patients with PCOS, who visited the hospital for treatment between April and July 2020. The presence of PCOS was diagnosed by a gynecologist based on the Rotterdam criteria[21] and clinical assessment. According to the Rotterdam scale, patients with PCOS should have two of the following three criteria: 1) Oligo/anovulation (oligomenorrhea [35–182 days] or amenorrhea [>182 days] and FSH 1–10 U/L, with normal E2, 2) hyperandrogenism (hirsutism [Ferriman–Gallwey score ≥9], and/or biochemical: free androgen index [FAI] > 4.5), 3) polycystic ovaries appearing on ultrasound (one or two ovaries >10 cm^3 and/or follicle count [2–9 mm]; one or two ovaries ≥12 follicles). Participants were recruited among PCOS patients 20 to 50 years old, and body mass index (BMI) between 18 and 30. Patients who suffered from any chronic diseases, adherence to a specific diet, pharmacological regime, supplement intake, or intention to adopt a specific physical activity program within the last 6 months that might influence outcomes of interest were excluded. The sample size was assessed using the formula suggested for clinical trials; considering type I error of 5% (α = 0.05) and type II error of 20% (β = 0.20; power = 80%). When the possible withdrawal of participants was taken into account, the number of participants increased to 80. To hide the identity of investigators and participants, both the randomization and allocation processes were conducted by a trained staff who was not part of the study's researchers. Random assignment was performed through a random number sheet generated by the Statistical Package for the Social Sciences (SPSS) software version 21. Signed written consent was taken from all participants at the commencement after they were informed about the study, its risks, and its benefits.

Study design

Patients who were eligible based on inclusion/exclusion criteria were randomly assigned to take either an 800 mg/day garlic pill (Goldaroo Company, Isfahan, Iran) or a placebo (starch) before lunch. They were also asked to avoid consuming any other supplement during the study period. Garlic and placebo were provided by the manufacturer in an encoded bottle, and neither researchers nor participants were aware of the content of the package until the data were analyzed. The appearance of garlic and placebo was identical in shape, color, size, odor, and package. Participants were followed by a phone interview once a week to monitor their compliance with the study schedule. They were also requested to keep their diet and physical activity unchanged throughout the study. In addition, dietary information was assessed by a 3-day food record (one weekend day and two non-consecutive weekdays) at baseline and end of the study. The dietary information was converted to nutrient intake for study participants via the Nutritionist 4 software (First Databank Inc., Hearst Corp., San Bruno, CA, USA). Physical activity was expressed as metabolic equivalents using a short form of the International Physical Activity Questionaries (IPAQ).

Biochemical assessment and anthropometric measures

To measure serum antioxidant variables, 10 mL of venous blood was taken from all participants after 12 to 14 h of fasting both at the beginning and the end of the study. The subjects' serum samples were isolated by centrifugation and stored at –70°C until the tests were performed. The total antioxidant capacity was measured using the method described by Rris *et al*.[22] The serum levels of malondialdehyde were also measured by a manual colorimetric test using thiobarbituric acid.[23] The catalase measurement method was based on the rate of decrease in the optical absorption of hydrogen peroxide due to its degradation by existing catalase in the sample.[24] To measure glutathione, the difference between calculated optical absorbance and the glutathione concentration in the sample was used in comparison with the standard of reduced glutathione.[25]

Weight and height were measured while participants wore the least number of clothing items and unshod using the Seca Scale (Seca Hamburg, Germany). BMI was calculated using the suggested formula. The waist circumference (WC) and hip circumference were assessed in the standing position using a conventional scale. Furthermore, the waist to hip circumference ratio (WHR) was calculated. Systolic and diastolic blood pressures were assessed in a relaxed sitting position after a minimum of 15-min rest using a mercury sphygmomanometer (ALPK2, Zhejiang, China; Datis Co., Tehran, Iran) over the right arm.

Statistical analysis

The data are presented as mean ± standard deviation (SD) and percentage for continuous and categorical variables, respectively. The normal distribution of data was analyzed using the Kolmogorov–Smirnov test. The difference between pre-and post-measures of demographic variables, habitual diet intake, physical activity, and the outcomes of interest in each group was assessed by paired *t*-test. To determine the difference in the change of outcomes of interest during the intervention period between the

two groups, an ANCOVA model was applied, in which the results were adjusted for potential confounders. All statistical analyses were performed with SPSS version 21 (SPSS Inc, Chicago, IL, USA) and the statistical significance was set at $P < 0.05$.

Results

All 80 patients who were randomly assigned to the garlic and placebo groups completed the trial, and their data were included in the final analysis [Figure 1]. The baseline characteristics of participants are shown in Table 1. There were no significant differences between garlic and control groups in anthropometric measures and blood pressure at baseline. In addition, no significant difference was observed between intervention and controls in terms of macronutrient intake, physical activity levels, and some minerals related to oxidative stress neither at the baseline nor at the end of the trial [Table 2]. No serious adverse effects resulting from garlic supplementation were reported by patients during the study.

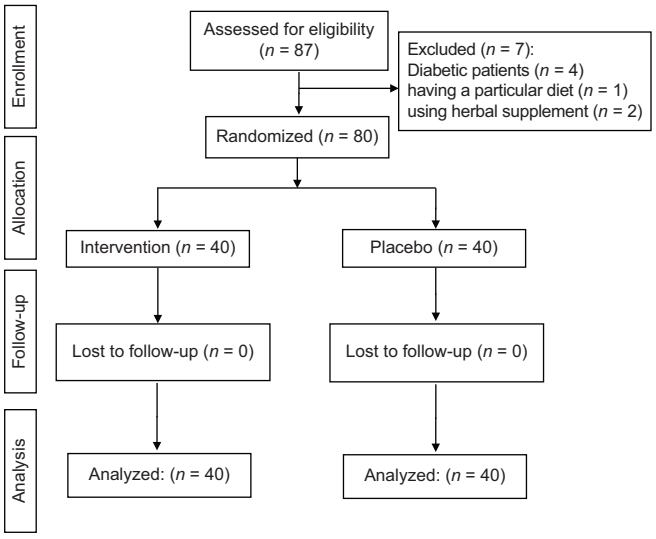

Figure 1: Participant flow diagram

Compared with placebo, garlic supplementation for 8 weeks resulted in a significant decrease in weight (–0.64 ± 1.94 vs. 0.11 ± 0.82; *P* value: 0.04), BMI (–0.25 ± 0.75 vs. 0.05 ± 0.61; *P* value: 0.04), and WC (–0.21 ± 0.77 vs. 0.02 ± 0.65; *P* value: 0.01). However, no significant change was detected in hip circumference (*P*-value: 0.26) and WHR (*P*-value: 0.87).

In addition, compared with placebo, changes in catalase (1.82 ± 9.28 vs. –1.55 ± 8.66; *P* value: 0.03) and glutathione concentrations (29.15 ± 57.53 vs. 2.42 ± 77.51; *P* value: 0.048) in the garlic group were also significantly different, whereas no significant difference was observed in the change in total antioxidant capacity (*P*-value: 31) and malondialdehyde levels (*P*-value: 0.20) between intervention and control groups [Table 3].

Discussion

The present clinical trial assessed the effect of 8-week of administration of garlic supplement on oxidative stress markers among patients with PCOS. The findings demonstrated that garlic supplementation improved catalase and glutathione levels as well as body weight, BMI, and WC. However, it did not affect the hip circumference WHR, total antioxidant capacity, and malondialdehyde concentrations.

Currently, PCOS has become one of the most frequent female hormone disorders. Women with PCOS are more prone to be at risk for several complications, namely insulin resistance, diabetes, and cardiovascular diseases, which make it a critical problem for patients and the healthcare system as well.[26,27] We found that garlic supplementation can decrease weight, BMI, and WC. However, the effect of garlic on the hip circumference and WHR was non-significant. In line with our findings, several studies showed that garlic intake can decrease weight gain or reduce body weight.[28,29] In a clinical trial conducted by Soleimani *et al.*[30] on 110 subjects with non-alcoholic fatty liver disease (NAFLD), 400 mg/day garlic administration

Table 1: General characteristics of participants in intervention and control groups at the baseline

Variables		Intervention	control	*P**
Age (year)		29.07±6.08	29.70±5.95	0.64
Rotterdam Criteria	Ovulatory dysfunction *N* (%)	22 (55%)	28 (70%)	0.24†
	Hyperandrogenism *N* (%)	27 (67.5%)	24 (60%)	0.64†
	Polycystic ovary *N* (%)	33 (82.5%)	30 (75%)	0.58†
Weight (kg)		70.12±12.18	68.73±13.53	0.62
BMI (kg/m^2)		26.71±4.87	26.35±5.20	0.75
Waist circumference (cm)		79.86±9.01	79.46±10.10	0.85
Abdomen circumference (cm)		95.06±10.85	94.88±11.52	0.94
Hip circumference (cm)		103.67±8.74	102.61±7.86	0.57
Systolic blood pressure (mmHg)		119.75±9.27	119.74±10.04	0.95
Diastolic blood pressure (mmHg)		78.47±8.16	79.57±9.89	0.89

Data are presented as mean±standard deviation (SD). **P*-value was obtained from independent Student's *t*-test. †*P*-value was obtained from independent Chi-square test

Table 2: Daily energy and macronutrient intake, and physical activity of participants, before and after the treatment period

Variables	Intervention (40)	Control (*n*=40)	*P**
Energy intake (kcal/day)			
Baseline	1904±506	2075±517	0.13
8th week	1849±520	2040±498	0.09
*P***	0.32	0.58	
Total carbohydrates (g/day)			
Baseline	241.56±71	270.03±82	0.10
8th week	232.31±66	257.66±78	0.12
*P***	0.39	0.63	
Total protein (g/day)			
Baseline	71.11±27	76.07±19	0.35
8th week	72.10±29	76.61±22	0.44
*P***	0.78	0.89	
Total-fat (g/day)			
Baseline	66.56±25	69.84±21	0.53
8th week	63.47±22	66.46±20	0.53
*P***	0.26	0.29	
Mono-unsaturated fatty acid (g/day)			
Baseline	21.79±8.26	23.17±7.83	0.64
8th week	22.32±8.54	23.66±8.28	0.28
*P***	0.59	0.68	
Poly-unsaturated fatty acid (g/day)			
Baseline	14.71±6.92	15.75±6.08	0.64
8th week	13.49±6.01	15.39±5.82	0.07
*P***	0.12	0.70	
Dietary fiber (g/day)			
Baseline	26.55±13.39	27.78±12.04	0.66
8th week	23.57±12.46	28.03±13.54	0.08
*P***	0.16	0.78	
Vitamin E (mg/day)			
Baseline	13.60±6.77	13.61±6.60	0.99
8th week	12.12±6.38	14.01±6.62	0.20
*P***	0.15	0.71	
Vitamin C (mg/day)			
Baseline	115.86±88.29	116.95±74.94	0.95
8th week	114.56±64.75	130.01±74.51	0.30
*P***	0.27	0.93	
Beta-carotene (µg/day)			
Baseline	3967±3622	3882±4747	0.81
8th week	4188±6800	3528±2146	0.03
*P***	0.84	0.10	
Chromium (mg/day)			
Baseline	0.046±0.036	0.055±0.054	0.82
8th week	0.052±0.035	0.058±0.043	0.17
*P***	0.34	0.72	
Selenium (mg/day)			
Baseline	81.41±25.82	83.26±30.90	0.77
8th week	83.47±36.29	87.53±30.64	0.44
*P***	0.67	0.38	
Zinc (mg/day)			
Baseline	9.30±3.70	10.19±3.41	0.26
8th week	9.07±3.36	10.55±3.80	0.06
*P***	0.62	0.29	
Physical activity (met/h/week)			
Baseline	20.25±2.7	21.41±3.5	0.10
8th week	22.68±2.8	23.52±3.1	0.20
*P***	0.12	0.31	

Data are presented as mean±standard deviation (SD). *Independent *t*-test. **Paired sample Student's *t*-test

led to weight reduction after 15 weeks. They also reported that this weight reduction was mainly for a decrease in body fat mass, not lean body mass. In addition, another study on patients with NAFLD, in which garlic aged power was administrated, showed a significant improvement in WC.[31] Several mechanisms are proposed for the anti-obesity properties of garlic that are attributed to its organosulfur ingredients. Thiacremonone, one of the garlic sulfur compounds, activates AMP-activated protein kinase, as a consequence, the expression of acetyl CoA carboxylase-1, which is an essential enzyme for regulating the cycle of fatty acid synthesis, is reduced.[32,33] Ajoene, another bioactive component of garlic, increases apoptosis in adipocytes via activating mitogen-activated protein kinases. In addition, 1,2-vinyldithiin (a garlic-derived organosulfur) suppresses the expression of the peroxisome proliferator-activated receptor (*PPAR*) gamma gene, which leads to the inhibition of human preadipocyte differentiation, and consequently to a reduction in lipid accumulation.[34] It has also been shown that garlic decreases the intestinal absorption of triglycerides and prevents weight gain.[35]

The present study revealed that garlic can also improve oxidative stress-related markers. In agreement with our findings, Mirunalini *et al.*[36] showed that the administration of 3.6 g/d garlic in diabetic patients led to an improvement in erythrocytes' superoxide dismutase, catalase, and glutathione peroxidase levels. Another study on pregnant women at risk for pre-eclampsia revealed an increase in plasma glutathione levels but did not significantly change the total antioxidant capacity.[37] However, a clinical trial conducted on 70 women with rheumatoid arthritis showed that consumption of 500 mg/d garlic for 8 weeks can improve both total antioxidant capacity and malondialdehyde levels.[38] The discrepancy between our findings and the results of the mentioned study might be due to the nature of the diseases and the baseline levels of variables. The main mechanism of the garlic antioxidant activity can be attributed to both the regulation of the Nrf2–ARE pathway which is a redox-sensitive transcription factor and can stimulate the expression of antioxidant

Table 3: The effect of 8-weeks garlic supplementation on oxidative stress profile

Variables	Intervention (*n*=40)			*P**	Placebo (*n*=40)			*P**	*P***
	Before	After	Change		Before	After	Change		
Weight	70.12±12.18	69.48±12.13	-0.64±1.94	0.044	68.73±13.53	68.84±13.60	0.11±0.82	0.642	0.042†
BMI	26.71±4.87	26.45±4.87	-0.25±0.75	0.039	26.35±5.20	26.41±5.26	0.05±0.61	0.574	0.040†
Waist circumference	79.86±9.01	79.65±8.91	-0.21±0.77	0.091	79.46±10.10	79.48±10.02	0.02±0.65	0.812	0.015†
Hip circumference	103.67±8.74	103.44±8.73	-0.22±0.97	0.151	102.61±7.86	102.64±7.94	0.03±1.04	0.856	0.261
Waist to hip circumference ratio	0.77±0.05	0.76±0.05	-0.003±0.008	0.760	0.77±0.10	0.77±0.10	0.0002±0.009	0.871	0.870†
Total antioxidant capacity	14.68±7.72	16.59±6.46	1.91±5.03	0.025	11.59±4.70	12.14±4.67	0.54±5.67	0.566	0.317
Catalase	24.55±15.10	26.38±15.13	1.82±9.28	0.233	20.25±6.68	18.70±7.00	-1.55±8.66	0.288	0.030
Glutathione peroxidase	224.80±70.23	253.95±56.33	29.15±57.53	0.003	229.86±63.34	232.29±60.87	2.42±77.51	0.852	0.048
Malondialdehyde	4.67±3.63	4.03±3.25	-0.63±4.40	0.365	4.17±3.63	5.08±2.88	20.90±4.30	0.190	0.208

Data are presented as mean±SD. *Paired sample Student's *t*-test. **Obtained from ANCOVA test, adjusted for age, BMI, energy intake, physical activity, and baseline measures. †Adjusted for age, energy intake, physical activity, and baseline measures

genes responsible for antioxidant enzymes, and elevation of antioxidant enzyme activities.[39,40] In addition, garlic, because of its sulfur-based substances such as allicin, s-allyl-cysteine, s-allyl-mercaptocysteine, and diallyl disulfide, has an intrinsic antioxidant property that has been widely documented by previous experimental studies. The redox-active sulfhydryl (SH)- or disulfide (-S-S)- residues of the mentioned ingredients can act as a free radical scavenger.[41] Furthermore, garlic's bioactive ingredient, or rather ajoene, is a human glutathione reductase substrate.[29]

Oxidative stress, which is the result of the overproduction of reactive oxygen species (ROS), can contribute to the development of obstetric complications.[42] The association between excess oxidative stress levels and early and recurrent pregnancy loss, preeclampsia, intrauterine growth restriction (IUGR), and preterm labor have been shown previously. ROS negatively influences embryo implantation and contributes to the development of endometriosis and preeclampsia.[43,44] In addition, excessive body weight has an adverse effect on the fecundability of females, fetuses, and embryos via oxidative mechanisms.[42,45] As these effects can be improved with the use of antioxidants, it might be postulated that garlic supplementation could be a promising treatment for patients with PCOS and minimize the risk of infertility.

The study has some limitations that should be taken into account. The duration of the study was approximately short. Although we found a promising effect even during this period of time, a longer intervention might lead to a higher beneficial effect. In addition, we tried to restrict confounders using adjustment for some variables that can potentially affect the results; however, there might be other potential confounders such as genetics, which we were unable to control.

Conclusions

The present study suggests that garlic supplementation might be beneficial on oxidative stress markers and anthropometric measures among patients with PCOS. Garlic is a safe natural food with broad health benefits that can be used for weight loss and improvement in antioxidant markers. However, further studies with larger sample size and longer duration are necessary to confirm our findings.

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Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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