

The Effect of Garlic (*Allium Sativum*) on Polycystic Ovary Syndrome Related Hormones and Glycemic Parameters: A Randomized, Double-Blinded Clinical Trial

Abstract

Background: The purpose of the present study was to investigate the effect of garlic supplementation on androgen levels and glycemic-related markers in patients with PCOS. **Methods:** In these 8 weeks of randomized double-blinded control trial, 80 women were randomly assigned into two groups in which patients were asked to intake either 800 mg/day garlic or an identical placebo. A blood sample was obtained pre- and post-trial to assess androgens and glycemic-related parameters. A 3-days- food record and a short form of international physical activity questionnaires (IPAQ) were also evaluated at the beginning and end of the trial. **Results:** All participants completed the trial. Garlic supplementation resulted in significant reduction in fasting plasma glucose (-3.22 ± 7.41 vs. 0.72 ± 5.37 ; $P = 0.008$) and homeostatic model assessment for insulin resistance (HOMA-IR) (-0.29 ± 1.45 vs. 0.28 ± 1.20 ; $P = 0.02$). In addition, a trend to a significant improvement was detected in free androgen index (FAI) ($P = 0.09$), insulin levels ($P = 0.07$), and quantitative insulin sensitivity check index (QUICKI) ($P = 0.06$). However, no significant difference was found in testosterone and sex hormone-binding globulin (SHBG) ($P > 0.05$). **Conclusions:** Present study indicates that garlic supplementation could be beneficial for FPG and insulin resistance improvement. However, garlic supplementation does not show remarkable efficacy on androgens. Further studies are warranted to confirm the results.

Keywords: Garlic, insulin resistance, polycystic ovary syndrome, testosterone

Introduction

Nowadays, polycystic ovary syndrome (PCOS) is known as a most gynecological endocrine condition affecting women childbearing age in both developed and developing countries.^[1] Its symptoms include a variety of reproductive and metabolic disorders such as arrested folliculogenesis, hyperandrogenism, polycystic ovaries, insulin resistance, and hyperlipidemia.^[2,3] The number of women suffering from PCOS account for a large proportion of the world population.^[4] PCOS etiology has not been clearly understood yet; however, genetics and environmental factors are proposed to be the most important contributor to the disease.^[5] Although the disease does not lead to mortality, the patients encounter several problems which substantially decrease their quality of life.^[6] Patients are also at risk for several chronic conditions such as diabetes type 2 and cardiovascular diseases.^[7] The main PCOS

treatment is based on the modification in lifestyle and using a medical approach such as clomiphene citrate administration and insulin-sensitizing agent.^[8,9] However, it does not seem to be sufficient as pharmacological agents are not without side effect, and change in lifestyle can be difficult for people.^[10] As a consequence, many researchers have become interested in finding an adjuvant remedy along with the common PCOS medical treatment.

Garlic (*Allium sativum*) is a biennial herb and belongs to the *Liliaceae* family, which has been used as a species around the world.^[11] It has been traditionally applied for medical use for years. It includes several bioactive component sulfur-containing compounds, namely alliin, allicin, diallyl trisulfide, and ajoene which make garlic a health-benefit agent with antimicrobial, antioxidant, cholesterol-lowering, blood thinning, and anti-aging properties.^[12,13] The medical properties of garlic have been shown in the improvement of diabetes.^[14] In

Roya Zadhoush,
Amirmansour
Alavi-Naeini,
Awat Feizi¹,
Elham Naghshineh²,
Mohammad Reza
Ghazvini³

Department of Community Nutrition, School of Nutrition and Food Science, Isfahan University of Medical Sciences, Isfahan, Iran, ¹Department of Biostatistics and Epidemiology, School of Public Health, Isfahan University of Medical Sciences, Isfahan, Iran, ²Department of Obstetrics and Gynecology, School of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran, ³Isfahan Center of Health Research, National Institute of Health Research, Isfahan, Iran

Address for correspondence:

Dr. Amirmansour Alavi-Naeini,
Department of Community Nutrition, School of Nutrition and Food Science, Isfahan University of Medical Sciences, PO Box: 8174673461, Isfahan, Iran.

E-mail: am.alavi@nutr.mui.ac.ir

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addition, previous studies indicated that garlic can improve oxidative stress and insulin resistance which seems to be involved in the onset and/or progression of PCOS.^[15,16] Thus, garlic might have a beneficial effect on this disease by modifying these markers.

Regarding aforesaid information which indicates the importance of investigation in this area and the paucity available information in this field, the present study was performed to evaluate the effect of garlic on PCOS-related hormones.

Methods

Participants

This randomized, double-blinded, controlled trial was carried out in Isfahan, from April to July 2020. Participants were selected among PCOS patients, aged between 18 to 45 and body mass index (BMI) less than 30 (kg/m²) who attended to hospital. PCOS was diagnosed based on Rotterdam criteria^[17] and clinical test. Patients who had chronic diseases, followed any special diet, physical activity program, and got any supplement and drug in the past 6 months which could influence PCOS markers, were excluded. The sample size was calculated by the suggested formula by considering type I error 0.05 and power 80%. The number of participants was raised to 80 to compensate 20% of possible attrition during the study.

The procedure of randomization and assignment was performed by a trained staff; hence, all participants and investigators were concealed to the allocation until the main analysis was completed. A random-generated number sheet, obtained by the Statistical Package for the Social Sciences (SPSS) software version 21, was applied for participants' random allocation.

Protocol

Present study was performed in accordance with the Declaration of Helsinki guideline.^[18] Before the study started, all participants were informed of the risk and benefits of the study, and they were asked to sign a written consent. Then, they were randomly divided into intervention and control groups. Participants in active arms were taught to consume an 800 mg/day garlic supplement, including a 300 and a 500 mg/day pills (GolDaroo Company, Isfahan, Iran) or placebo (two pills containing starch) which was similar in shape and odor after lunch for 8 weeks. The compliance to schedule was checked weekly by phone interview. They were asked to maintain their usual diet and physical activity during the study. Also, their habitual diet and physical activity were monitored by a 3-nonconsecutive-day food record and a short form of international physical activity questionnaires (IPAQ), respectively.

Anthropometric measures

Weight and height were assessed using a digital scale (Seca, Hamburg, Germany) and a non-stretch tape measure (Seca, Hamburg, Germany), respectively, with the minimum wearing clothes without shoes. Body mass index (BMI) was calculated based on a relevant formula. The waist circumference (WC) was measured in a standing position from the lowest rib to the extremity of the pelvic bone fracture using an anthropometric meter. The hip circumference was measured in a standing position from the most prominent part of the buttocks. In addition, the waist-to-hip circumference ratio (WHR) was also calculated. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured by a mercury sphygmomanometer (ALPK2, Zhejiang, China; Davis Co, Tehran, Iran) over the right arm, while participants got rest on the chair for a minimum of 15 minutes.

Biochemical assessment

In biochemical assessment, a 10 ml blood sample was collected after overnight fasting at the beginning and end of 8 weeks' intervention. Then serums were extracted and stored at -70°C before analysis in the laboratory. Fasting plasma glucose was assessed with the conventional kit (Pars Azmoon Company, Iran) by a Hitachi 902 biochemical analyzer. Insulin was measured by an enzyme immunoassays kit (Pars Azmoon Company, Iran). The homeostatic model assessment of insulin resistance (HOMA-IR) {fasting insulin (μmol/L) × FPG levels (mg/dl)/405} and the quantitative insulin sensitivity check index (QUICKI) {1/[log fasting insulin (μU/ml) + log fasting glucose (mg/dl)]} were calculated by conventional formula. Serum testosterone, free androgen index (FAI), and sex hormone-binding globulin (SHBG) were assessed using commercial validated kits (Pars Azmoon Company, Iran).

Statistical analysis

Statistical analysis was performed using SPSS version 21 (SPSS Inc, Chicago, IL, USA). The Kolmogorov–Smirnov test was used to determine the normal distribution of data. The paired t-test was used to determine the difference in general information, physical activity, and nutrient intake between the intervention and control groups. A multiple adjustment test by using the ANCOVA test was applied to compare the difference of outcomes' changes between the two groups. *P* value <0.05 was considered significant.

Results

A total of 80 PCOS patients were eligible and randomly allocated to the either intervention or control group. All of them completed the study, and information from all participant was included to the analysis [Figure 1].

Table 1 shows the participants' general information at the beginning of the study. There was no significant difference in age, anthropometric measures, and blood pressure between garlic and the control groups. Likewise, no significant difference was detected between the intervention and control groups regarding nutrients, vitamins, and physical activity at both baseline and end of the study [Table 2].

Table 3 presents the hormone assessment in garlic and placebo groups at pre- and post-intervention. Compared to placebo, garlic administration for 8 weeks resulted in a significantly reduced FPG concentrations (-3.22 ± 7.41 vs. 0.72 ± 5.37 ; $P = 0.008$) and HOMA-IR (-0.29 ± 1.45 vs. 0.28 ± 1.20 ; $P = 0.02$). Furthermore, a trend to a significant decrease was found in insulin levels (-0.65 ± 6.01 vs. 1.25 ± 5.01 ; $P = 0.07$), QUICKI (0.001 ± 0.2 vs. -0.007 ± 0.02 ; $P = 0.06$), and FAI (-0.63 ± 2.48 vs. 0.20 ± 0.71 ; $P = 0.09$). However, we failed to find any significant difference between garlic and placebo groups in testosterone concentrations (-0.07 ± 0.41 vs. 0.06 ± 0.32 ; $P = 0.19$) and SHBG 10.56 ± 44.90 vs. -3.71 ± 46.52 ; $P = 0.24$).

Discussion

The present study was the first trial that assessed the effect

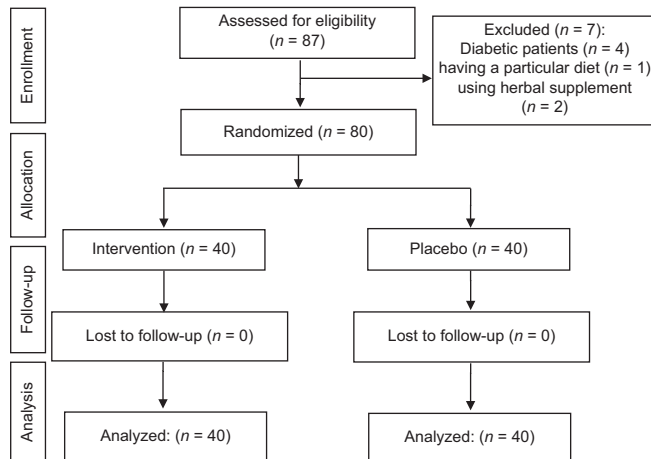


Figure 1: Participant flow diagram

Table 1: Participants' characteristics in intervention and control groups at the baseline

Variables	Intervention	Control	P*
Age (year)	29.07±6.08	29.70±5.95	0.64
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±SD. *P-value was obtained from independent Student's *t*-test

of garlic administration on PCOS markers. The results indicated that garlic supplementation can mitigate FPG and HOMA-IR. In addition, insulin levels, QUICKI, and FAI showed a trend to a significant decrease after 8-week

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
8 th 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
8 th week	232.31±66	257.66±78	0.12
P**	0.39	0.63	
Protein (g/day)			
Baseline	71.11±27	76.07±19	0.35
8 th 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
8 th week	63.47±22	66.46±20	0.53
P**	0.26	0.29	
MUFA (g/day)			
Baseline	21.79±8.26	23.17±7.83	0.64
8 th week	22.32±8.54	23.66±8.28	0.28
P**	0.59	0.68	
PUFA (g/day)			
Baseline	14.71±6.92	15.75±6.08	0.64
8 th 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
8 th 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
8 th 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
8 th 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
8 th week	4188±6800	3528±2146	0.03
P**	0.84	0.10	
Physical activity (met/h/week)			
Baseline	20.25±2.7	21.41±3.5	0.10
8 th week	22.68±2.8	23.52±3.1	0.20
P**	0.12	0.31	

Data are presented as Mean±SD. *Independent *t*-test. **Paired sample Student's *t*-test.

Table 3: Effect of 8-week garlic supplementation on androgens and glycemic-related markers

Variables	Intervention (n=40)			P*	Placebo (n=40)			P*	P**
	Before	After	Change		Before	After	Change		
Testosterone	0.70±0.27	0.63±0.37	-0.07±0.41	0.32	0.58±0.41	0.65±0.44	0.06±0.32	0.22	0.190
Sex hormone-binding globulin (SHBG)	48.93±35.26	59.50±54.14	10.56±44.90	0.17	72.51±79.89	68.80±59.47	-3.71±46.52	0.64	0.241
Free androgen index (FAI)	2.42±2.31	1.78±1.54	-0.63±2.48	0.13	1.33±1.26	1.54±1.40	0.20±0.71	0.10	0.097
Fasting plasma glucose	92.92±6.74	89.70±5.40	-3.22±7.41	0.009	90.25±7.51	90.97±4.67	0.72±5.37	0.399	0.008
Fasting insulin	12.88±7.08	12.22±5.67	-0.65±6.01	0.497	12.23±5.64	13.49±5.41	1.25±5.01	0.122	0.074
HOMA-ir	2.99±1.75	2.69±1.23	-0.29±1.45	0.208	2.76±1.36	3.05±1.27	0.28±1.20	0.145	0.028
QUICKI	0.33±0.02	0.33±0.02	0.001±0.2	0.789	0.32±0.02	0.33±0.03	-0.007±0.02	0.045	0.062

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

garlic administration. Nevertheless, no significant efficacy resulted from garlic administration was observed on SHBG and testosterone concentrations.

These days, PCOS has become one of the most sex-related diseases among women that has a lot of complications.^[19] Indeed, not only does PCOS suffer patients by its maladaptive effect on metabolites, it can decrease patients' quality of life, as well.^[5,20] This makes PCOS an important disorder that needs to find effective treatment. In the present study, we failed to find an effective influence of garlic on PCOS-related hormones, only FAI showed that it tends to be decreased by supplementation. No previous study investigated the garlic effect on testosterone levels; however, the beneficial effect of antioxidants has been previously documented. Rajan *et al.*^[21] reported that soy isoflavones' intake for 14 days can lead to a decrease in testosterone levels of PCOS-induced rat model. Moreover, it has been shown that change in gut microbiota by probiotic bacteria can improve androgen.^[22] As garlic can act as a pre-biotic and modify the intestinal microbiome population, it might decrease the testosterone levels and improve PCOS.

It has been reported that there is a direct association between insulin resistance and excessive amounts of insulin and raised ovarian production of androgens.^[23] Indeed, high insulin concentrations have a synergic effect with LH to increase androgen production. In addition, this adverse effect by abnormal insulin levels can be concurrent with inhibition of hepatic synthesis of SHBG.^[24] As SHBG is a protein that binds to testosterone, its lack of enough production can lead to an increase in free testosterone; consequently, it can cause several hormonal complications that are manifested in PCOS.^[23,25] Therefore, it can be expected that garlic, by modifying the insulin resistance, can mitigate androgen abnormality and improve PCOS.

We revealed that garlic can improve FPG and insulin resistance. Indeed, its efficacy on glycemic-related markers has been well-documented in people with other health problems such as diabetes and metabolic syndrome. Sobenin *et al.*^[26] indicated that 150 mg/day garlic administration for four weeks led to decrease in serum glucose in diabetic

patients. They also reported that garlic showed more efficacy than sulfonylureas in metabolic improvements. Such that, intake of raw garlic with the amount of three cloves per day showed a significant improvement in FPG among type 2 diabetic patients.^[27] Another study conducted by Choudhary *et al.*^[28] indicated that garlic has beneficial effect on component of metabolic syndrome such as FPG. Although some clinical trials did not find significant improvement on insulin resistance resulted by garlic intake^[15] which were in contrast to our findings, animal studies showed garlic stimulated insulin secretion^[29-31] and decreased insulin resistance.^[32] This controversy between human and animal studies might be due to the difference amount of garlic administration per body weight, and it is possible that improvement in insulin resistance could be observed by increasing the dosage of garlic intervention.

It has been suggested that garlic's beneficial effect on glycemic markers is mainly attributed to its sulfur base active components including allicin, alliin, diallyl disulfide, ajoene, etc.^[33] Allicin, one of the main garlic active ingredients, is responsible for the improvement in the pancreatic islets in type 2 diabetes^[34] and even regenerates beta cell.^[35] which consequently can enhance insulin secretion. Moreover, due to the free sulfur group, allicin also could elevate insulin activity.^[36] Garlic also decreases serum glucose by limiting glucose absorption from the intestine.^[37]

In the present study, no adverse effect was reported by patients which might be resulted from garlic administration. Garlic is generally safe, and its safety was approved by the US Food and Drug Administration (FDA). It only can cause bad breath, body odor, and gastric irritation in common dosage among healthy individuals. However, a high dose of garlic can lead to serious health problems such as bleeding, hypotension, and allergic reaction among people with susceptible health conditions.^[38]

The present study has several limitations which should be considered. The main limitation was the duration of the study which might not be enough to reach significant change in all variables, considering some outcomes tend to be significant. However, even in this period, we found a significant reduction in FPG and HOMA-IR. Further

studies with longer duration may gain better results. In addition, we could not assess the other hormones and ultrasound for polycystic ovarian which could potentially better reflect the PCOS condition. Future investigation can provide better insight into PCOS improvement through evaluating mentioned parameters.

Conclusions

The results from the current study suggest that garlic might improve FPG and insulin resistance in PCOS patients. It could be a promising adjuvant therapy which can be used along with pharmacological therapy to mitigate complications resulted from PCOS. However, further studies are warranted to confirm our results.

Acknowledgments

The study protocol was approved by the Ethics Committee of Isfahan University of Medical Science (IR.MUI.RESEARCH.REC.1399.806) and registered at the Iranian Registry of Clinical Trials with the following code: IRCT20161203031212N2. The authors would like to thank all the clinical staff of Amin Hospital and the study participants. They are also grateful to Goldaroo company for their support and cooperation.

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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