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RESEARCH ARTICLE

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The effect of garlic (*Allium sativum*) supplementation on the lipid parameters and blood pressure levels in women with polycystic ovary syndrome: A randomized controlled trial

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Polycystic ovary syndrome (PCOS) is the most prevalent female endocrine-related disorder in reproductive ages. The aim of the study was to investigate the effect of garlic on the lipid parameters and blood pressure levels in women with PCOS. The present study was a randomized, double-blinded control trial, conducted on 80 PCOS patients. Participants were taught to intake either a total 800 mg/day garlic supplement or an identical placebo (starch) after lunch for 8 weeks. Physical activity, diet intake, anthropometric measures, and blood pressure were evaluated at baseline and end of the study. The blood sample was also taken to assess the change in outcomes of interest at the pre- and post-intervention. Garlic supplementation significantly reduced serum total cholesterol (change mean difference: −8.05, 95% CI: −15.47, −0.62) and LDL-C (change mean difference: −7.67, 95%CI: −14.64, −0.70) levels in comparison to the control group. In addition, a trend to a significant decrease was found in serum triglyceride levels and Systolic blood pressure; however, no significant difference was observed between two groups in HDL-C and diastolic blood pressure levels. The present study suggested that garlic supplementation might be effective on lipid markers improvement. Further studies are needed to confirm our findings.

KEYWORDS
garlic, PCOS, polycystic ovary syndrome, serum lipids

1 | INTRODUCTION

Polycystic ovary syndrome (PCOS) is the most prevalent female endocrine-related disorder in reproductive ages, which affected 10–20% of women worldwide (Picton & Balen, 2019). It is characterized by disruption in sex hormone levels, and its clinical manifestations are irregular menstrual cycles, acne, male-patterned hair loss, and polycystic ovaries (March et al., 2010). The etiology of PCOS is not clearly documented to date; however, several factors including genetics, lifestyle are proposed to involve in the onset/progress of the disease (Karimi et al., 2020; Norman, Davies, Lord, & Moran, 2002). The patients also suffer from metabolic dysfunction such as dyslipidemia which can subsequently lead to metabolic syndrome, cardiovascular diseases, and myocardial infarction (Wild, 2012). PCOS has a substantial medical cost and imposes a huge burden on the health care system, directly and indirectly; therefore, finding new solutions, which can improve the diseases and their complications as well, remains a challenge for medical investigators (Hoeger, Dokras, & Piltonen, 2020; Witchel, Burghard, Tao, & Oberfield, 2019).

Garlic (*Allium sativum* L.) is an aromatic herbaceous annual spice, belonging to the Amaryllidaceae family that has a pivotal place in traditional medicine (El-Saber Batiha et al., 2020). It has been used from ancient times for the treatment of varying diseases including influenza, cold, and hypertension (Ayaz & Alpsoy, 2007; Badal et al., 2019). Gallic is rich in multiple bioactive components such as alliin, allicin, E- and Z-ajoene, 2-vinyl-4H-1,3-dithiin, diallyl sulfide

(DAS), diallyl disulfide (DADS), diallyl trisulfide (DATS), allyl methyl sulfide (AMS), s-allyl cysteine, s-methyl cysteine, and different polyphenols (Shang et al., 2019). The previous investigation suggested that it has cardiovascular protective activity (Drobiova et al., 2011) and can be a favorite for the immune system (Jang et al., 2018) as well as preventing inflammation (You, Yoo, Baek, & Kim, 2019) and cancer (Li, Le, & Cui, 2018). Furthermore, imperial studies have been indicated that garlic can improve total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C) among hyperlipidemic or cardiovascular at-risk patients via suppressing lipid biosynthesis (Jung et al., 2014; Sun, Wang, & Qin, 2018). The garlic's role in serum lipids improvement might make it a potential candidate for improving lipid parameters levels in other diseases.

Functional foods and medicinal plants have traditionally been used for lipid markers regulations (Cho et al., 2003). The beneficial impact of functional food such as flaxseed (Haidari, Banaei-Jahromi, Zakerkish, & Ahmadi, 2020) and curcumin (Mohammadi, Kayedpoor, Karimzadeh-Bardei, & Nabiuni, 2017) on blood glucose-related markers in PCOS patients has been imperially recommended, yet the effect of garlic on those markers has not been investigated. In this regard, the present study was performed to investigate the effect of garlic supplementation on serum lipid markers and blood pressure levels in women with PCOS.

2 | METHODS

2.1 | Subjects

This was a randomized controlled trial, conducted on PCOS patients, aged 18–45 years and with BMI less than 30, who were referred to the hospital between April and July 2020. The presence of PCOS was confirmed by a gynecologist based on clinical assessment and Rotterdam criteria (Broekmans et al., 2006), such that, PCOS was diagnosed if they had at least 2 out of 3 of following factors: (a) oligomenorrhea or amenorrhea; (b) hyperandrogenism which is determined by increasing androgens in the blood through biochemical or clinical symptoms; and (c) having polycystic ovaries appear on ultrasound. Participants were excluded if they had chronic diseases such as diabetes, renal failure, cardiovascular disease, autoimmune disease, and thyroid disorder, followed a specific diet, any supplement intake that can be effective on the outcomes, pregnancy, and breastfeeding. The sample size was calculated using the suggested formula by considering a type I error of 0.05, a power of 80%, an effect size of 21 (mg/dl), and a *SD* of 32 to determine a clinically meaningful in total cholesterol (TC) level which was obtained from previous studies (Garg et al., 2015; Koseoglu, Isleten, Atay, & Kaplan, 2010). The number of participants was raised to 80 to compensate 20% of possible attrition during the study. The randomization and assignment process was performed by an expert who was not involved with the study using a random number sequence, generated with the Statistical Package for the Social Sciences (SPSS) software version 21; therefore, the allocation concealment of participants, as well as investigators, was guaranteed until the study was completed. The study procedure was in accordance with the Helsinki declaration (Czarkowski, 2014). The study protocol was registered at IRCT (register ID: IRCT20161203031212N2) and was also confirmed by the ethical committee of Isfahan University of Medical Science (Cod ID: IR.MUI.RESEARCH.REC.1398.187).

2.2 | Study process

Eligible subjects were randomly allocated to either the intervention or control group. Patients were trained to get a total 800 mg/day garlic supplement- which was consisted of 300 and 500 mg pills to make the supplement smaller and more edible (GolDaroo Company, Isfahan, Iran) or placebo (two pills containing starch) after lunch for 8 weeks. The garlic supplement and placebo were identical in shape, color, and flavor, and their bottle was encoded by the manufacture to ensure both researchers and participants were blinded for intervention. To ensure subjects' compliance to the treatment, they were followed by investigators through a weekly phone call. In addition, they were asked to take back the supplement they did not consume to evaluate their adherence to the study procedure. Participants were also reminded to maintain their usual diet and physical activity unchanged, report any uncomfortable feelings during the study. Signed written consent was obtained from all participants at the commencement of the study.

2.3 | Anthropometric, diet, and physical activity assessment

Anthropometric measures were performed, after overnight fasting with minimal clothes and unshod by conventional means. Weight and height were assessed by a digital scale (Seca, Hamburg, Germany) and a non-stretch tape measure (Seca, Hamburg, Germany), respectively. BMI was calculated by the suggested formula (weight [Kg]/height squared [m^2]).

In addition, participants' dietary intake and physical activity were measured at the beginning and end of the study to check for any change in these parameters. Dietary intake was assessed using a 3-day food record (two non-consecutive weekdays and one weekend day). Then data were analyzed using the Nutritionist 4 software (First Databank Inc., Hearst Corp., San Bruno, CA, USA). Physical activity levels were also calculated by a short form of international physical activity questionaries' (IPAQ) (Moghaddam et al., 2012) and presented in met/h/week.

2.4 | Biochemical and blood pressure assessment

A fasting venous blood sample was obtained from all participants at pre- and post-intervention. After the samples were centrifuged, the plasma samples were extracted and kept at −70°C until biochemical measurements. Plasma lipid parameters including TC, triacylglycerol (TG), low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C) were assessed by using commercial kits (Pars-Azmoon, Tehran, Iran).

Blood pressure including systolic blood pressure (SBP) and diastolic blood pressure (DBP) was also measured at the beginning and end of the study after 15 min rest, while the participants sit on a chair in a relaxed situation by a mercury sphygmomanometer (ALPK2, Zhejiang, China; Datis Co, Tehran, Iran) over the right arm.

2.5 | Statistical analysis

The normal distribution of data was confirmed by the Kolmogorov–Smirnov test. Data were presented as mean ± *SD* or percent based on the nature of the variables. The difference in general characteristics between intervention and control was measured by independent *t*-test and chi-square test for numerical and categorical data, respectively. A similar analysis was also performed for assessing any difference in macronutrient intake as well as physical activity levels between two groups in pre- and post-intervention. Multiple adjustment approach by using ANCOVA test was applied to determine whether the difference of changes in outcomes of interest are significant between two groups. Statistical analysis was performed by the SPSS software version 21, and a *p*-value less than .05 was considered statistically significant.

3 | RESULTS

Of 88 PCOS patients who responded to our recruitment, 80 patients met inclusion/exclusion criteria and randomly assigned to either intervention or placebo group. All participants completed the treatment phase and their information was included in the final analysis (Figure 1).

Table 1 presents the participants' demographic characteristics information at baseline. There was no remarkable difference between the two groups regarding age, anthropometric measures, and SBP and DBP levels.

Table 2 shows the dietary intake and physical activity levels in the treatment group and placebo at the beginning and end of the study. There is no difference between pre-and post-intervention measures in either group in terms of total energy, macronutrients, vitamin E, vitamin C, chromium, beta-carotene intake, and physical activity. No serious adverse effect related to garlic intake was reported by participants throughout the study. Furthermore, the adherence of participants was more than 90% for both groups.

A multivariable analysis adjusted for age, BMI, energy, and physical activity showed that garlic supplementation resulted in a significant decrease in TC (change mean difference: −8.05, 95% CI: −15.47, −0.62, adjusted *p*-value: .036) and LDL-C (change mean difference: −7.67, 95% CI: −14.64, −0.70, adjusted *p*-value: .042) levels in compared to placebo. In addition, a trend to a significant reduction in TG levels (change mean difference: −10.67, 95% CI: −21.60, 0.25, adjusted *p*-value: .084) was found in the intervention group compared

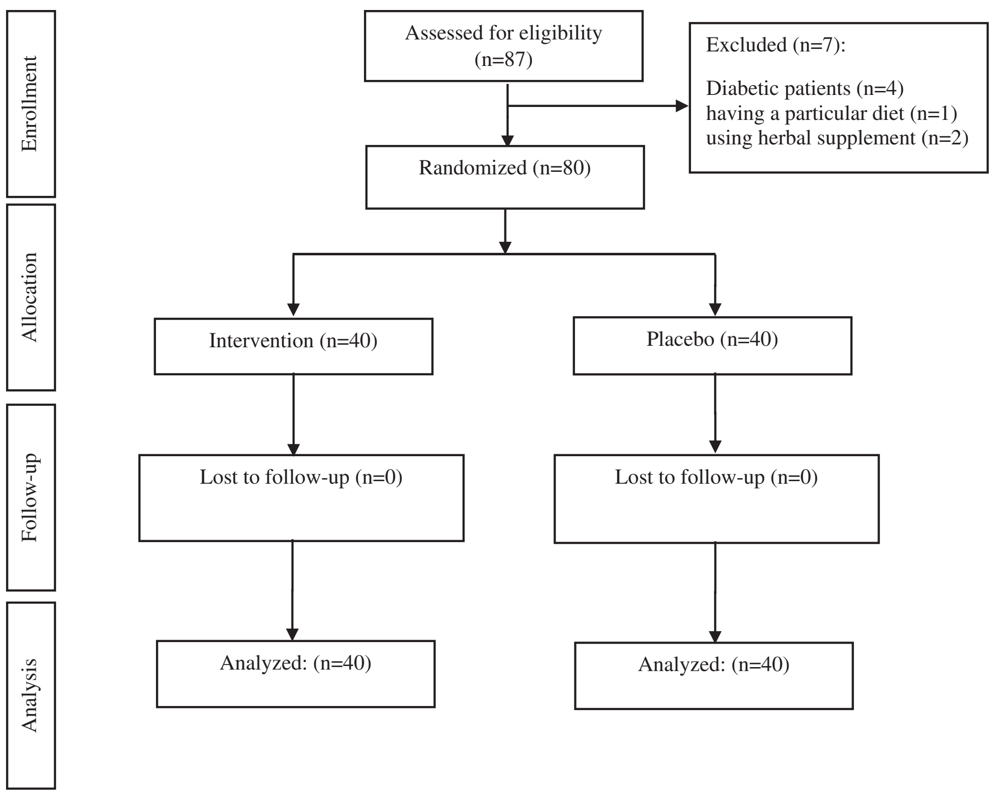

FIGURE 1 Participant flow diagram

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

Variables	Intervention	Control	*p*-value*
Age (year)	29.07 ± 6.08	29.70 ± 5.95	.644
Weight (kg)	70.12 ± 12.18	68.73 ± 13.53	.629
BMI (kg/m^2)	26.71 ± 4.87	26.35 ± 5.20	.752
Waist circumference (cm)	79.86 ± 9.01	79.46 ± 10.10	.852
Hip circumference (cm)	103.67 ± 8.74	102.61 ± 7.86	.571
Systolic blood pressure (mmHg)	119.75 ± 9.27	119.74 ± 10.04	.998
Diastolic blood pressure (mmHg)	78.47 ± 8.16	79.57 ± 9.89	.590

Note: Data are presented as mean ± *SD*.
**p*-value was obtained from the independent Student *t* test.

to the control. No significant change in HDL-C (change mean difference: 0.87, 95% CI: −1.42, 3.17, adjusted *p*-value: .385) was observed between the two groups.

The difference in SBP changes between the garlic and placebo group were nearly significant (change mean difference: −2.42, 95% CI: −5.76, 0.91, adjusted *p*-value: .071); however, a similar effect was not found in DBP (change mean difference: −0.82, 95% CI: −3.31, 1.66, adjusted *p*-value: .464) (Table 3).

4 | DISCUSSION

The present study which investigated the effect of garlic supplementation for 8 weeks on lipid profile levels and blood pressure among PCOS patients suggested that garlic reduces TC and LDL-C levels. In addition, a marginal improvement in TG and SBP was also observed; however, we failed to find any difference in HDL-C and DBP between the two groups.

Many women around the world are affected by PCOS, indeed, not only does the disease result in a decrease in self-esteem and increase anxiety among PCOS patients but also make them at risk for chronic diseases such as diabetes and cardiovascular diseases (Azziz et al., 2016; Pachiappan, Matheswaran, Saravanan, & Muthusamy, 2017). Despite substantial progress that has been made in the treatment of the disease, change in lifestyle remains is the main recommendation, and finding an adjuvant cure to help the treatment process has remained an essential need (Patel, 2018). We found that garlic supplementation can improve TC and LDL-C levels. in addition, a tendency to a significant reduction in TG was also observed. Similar to our study, several empirical studies have shown that garlic can be effective on lipid parameters. In line with the present study, Kojuri, Vosoughi, and Akrami (2007) reported that garlic can be useful for lipid profile improvement. In this study, 50 hyperlipidemic patients were administrated with enteric-coated garlic powder tablets for 6 weeks. At the end of the study, a significant improvement in TC, LDL-C, and HDL-C was observed in the garlic group compared to placebo. Similarly, another study suggested a significant improvement in TG, TC, LDL-C, and HDL-C resulted in 12 weeks of garlic administration (Sangouni, Mohammad Hosseini Azar, & Alizadeh, 2020). In the contrast, a study conducted by Peleg et al. (2003) did not show any significant effect of 16 weeks of administration with garlic in the form of alliin 22.4 mg/day on TC, TG, LDL-C, and HDL-C among people with mild to moderate hypercholesterolemia. The reason behind these discrepancies is unclear. It might be due to differences in participants' health conditions. The mechanisms underlying the antihyperlipidemic properties of garlic are not clearly identified. It seems that garlic bioactive components and phytochemicals improve lipid profile by suppressing the hepatocellular cholesterol biosynthesis and protecting both LDL-C and HDL-C from oxidation (Hosseini & Hosseinzadeh, 2015). It also reduces TC levels by an increase in TC excretion (Qidwai & Ashfaq, 2013). In addition, mitigating lipid peroxidation, which is a common benefit role among nutrients, functional foods and medicinal plants (Akbari-Fakhrabadi, Heshmati, Sepidarkish, & Shidfar, 2018; Heshmati et al., 2019; Loloei et al., 2019) is a another garlic favorable impact on lipid profile. It has been proposed that garlic can decrease stress oxidative and prevent lipid peroxidation by scavenging superoxide radicals, free radicals of iron, and reactive oxygen species either by enhancing oxidative defense system such as glutathione peroxidase or through its phenolic components (Das & Saha, 2009; Davidović-Plavšić, Kukavica, Škondrić, Jimenez-Gallardo, & Žabić, 2021; Nuutila, Puupponen-Pimiä, Aarni, & Oksman-Caldentey, 2003).

The present study revealed that SBP tends to be improved after garlic administration; however, we failed to find any significant effect on DBP. Empirical studies have been shown a promising influence of garlic on blood pressure. It has been revealed that intake of 100 mg/kg/bodyweight raw crushed garlic twice a day for 4 weeks can decrease SBP and DBP in metabolic syndrome patients (Wlosinska et al., 2020). Likewise, results by another study indicated that after 12 weeks of intervention by 960 mg garlic extract blood pressure remarkably improved in hypertension patients (Ried, Frank, & Stocks, 2010). The main cause of inconsistency between our findings and these studies might be due to the bassline blood pressure levels as both mentioned studies conducted on hypertensive patients. Several mechanisms are attributed to garlic's normotensive role. It has been proposed that garlic can decrease blood pressure by reducing peripheral vascular resistance through its prostaglandin-like effect. Also, γ-glutamyl cysteine, a bioactive ingredient of garlic, can alleviate blood pressure via suppressing angiotensin-converting enzymes. Moreover, allicin can elevate the elasticity of blood vessels as well as

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-value*
Energy intake (kcal/day)	Baseline	1904 ± 506	2075 ± 517	.139
	8 weeks	1849 ± 520	2040 ± 498	.098
	p-value**	.321	.582	
Total carbohydrates (g/day)	Baseline	241.56 ± 71	270.03 ± 82	.103
	8 weeks	232.31 ± 66	257.66 ± 78	.121
	p-value**	.395	.632	
Total protein (g/day)	Baseline	71.11 ± 27	76.07 ± 19	.359
	8 weeks	72.10 ± 29	76.61 ± 22	.442
	p-value**	.784	.891	
Total-fat (g/day)	Baseline	66.56 ± 25	69.84 ± 21	.532
	8 weeks	63.47 ± 22	66.46 ± 20	.537
	p-value**	.264	.298	
Mono-unsaturated fatty acid (g/day)	Baseline	21.79 ± 8.26	23.17 ± 7.83	.644
	8 weeks	22.32 ± 8.54	23.66 ± 8.28	.280
	p-value**	.598	.681	
Poly -unsaturated fatty acid (g/day)	Baseline	14.71 ± 6.92	15.75 ± 6.08	.641
	8 weeks	13.49 ± 6.01	15.39 ± 5.82	.078
	p-value**	.126	.702	
Dietary fiber (g/day)	Baseline	26.55 ± 13.39	27.78 ± 12.04	.664
	8 weeks	23.57 ± 12.46	28.03 ± 13.54	.085
	p-value**	.160	.785	
Vitamin E (mg/day)	Baseline	13.60 ± 6.77	13.61 ± 6.60	.997
	8 weeks	12.12 ± 6.38	14.01 ± 6.62	.202
	p-value**	.157	.716	
Vitamin C (mg/day)	Baseline	115.86 ± 88.29	116.95 ± 74.94	.956
	8 weeks	114.56 ± 64.75	130.01 ± 74.51	.301
	p-value**	.272	.933	
Beta-carotene (μg/day)	Baseline	3,967 ± 3,622	3,882 ± 4,747	.813
	8 weeks	4,188 ± 6,800	3,528 ± 2,146	.037
	p-value**	.844	.101	
Chromium (mg/day)	Baseline	0.046 ± 0.036	0.055 ± 0.054	.824
	8 weeks	0.052 ± 0.035	0.058 ± 0.043	.171
	p-value**	.346	.725	
Physical activity (met/hr/week)	Baseline	20.25 ± 2.7	21.41 ± 3.5	.102
	8 weeks	22.68 ± 2.8	23.52 ± 3.1	.201
	p-value**	.122	.310	

Note: Data are presented as mean ± *SD*.
*Independent *t*-test.
**Paired sample Student *t* test.

reducing in blood viscosity, consequently, both SBP and DBP will be diminished (Banerjee & Maulik, 2002; Choudhary & Jani, 2016).

No adverse effect related to garlic intake was reported by patients throughout the study. The garlic supplement is considered safe for humans by the US Food and Drug Administration (FDA); however, it can induce gastric agitation, particularly among susceptible people with a history of gastrointestinal problems. High-dose consumption of garlic can lead to several health problems such as diarrhea, nausea and vomiting, hypotension, bloating and flatulence, dizziness, headache, heartburn, and tachycardia (Rana, Pal, Vaiphei, Sharma, & Ola, 2011). Furthermore, a high amount of raw garlic intake for a long time can cause stomach injury and anemia (Mathew & Biju, 2008). Nonetheless, no negative side effects have been observed in routine dosage.

TABLE 3 The effect of 8 weeks garlic supplementation on lipid profiles and blood pressure

Variables		Intervention ($n = 40$) mean ± *SD*	Placebo ($n = 40$) mean ± *SD*	Diff[a]	95% CI Lower	95% CI Upper	p^b	p^c
Triglyceride	Pre	121.02 ± 52.84	116.12 ± 52.29	4.90	−18.50	28.30	.678	.084
	Post	112.65 ± 46.56	118.42 ± 48.53	−5.77	−26.94	15.39	.589	
	Change	−8.37 ± 26.62	2.30 ± 22.27	−10.67	−21.06	0.25	.055	
Total cholesterol	Pre	178.27 ± 26.34	174.60 ± 28.45	3.67	−8.53	15.88	.551	.036
	Post	173.00 ± 17.61	177.37 ± 26.18	−4.37	−14.30	5.58	.383	
	Change	−5.27 ± 17.54	2.77 ± 15.75	−8.05	−15.47	−0.62	.034	
LDL-C	Pre	96.40 ± 23.66	99.80 ± 22.39	−3.40	−13.65	6.85	.511	.042
	Post	91.02 ± 17.05	102.10 ± 20.80	−11.07	−19.54	−2.60	.011	
	Change	−5.37 ± 17.19	2.30 ± 13.96	−7.67	−14.64	−0.70	.031	
HDL-C	Pre	50.67 ± 9.61	53.25 ± 10.82	−2.57	−7.13	1.98	.264	.385
	Post	51.22 ± 9.63	52.92 ± 10.13	−1.70	−6.10	2.70	.444	
	Change	0.55 ± 4.68	−0.32 ± 5.61	0.87	−1.42	3.17	.452	
Systolic blood pressure	Pre	119.75 ± 9.27	119.75 ± 10.04	0.00	−4.30	4.32	.998	.071
	Post	117.80 ± 6.78	120.22 ± 9.56	−2.42	−6.11	1.26	.195	
	Change	−1.95 ± 7.39	0.47 ± 7.58	−2.42	−5.76	0.91	.152	
Diastolic blood pressure	Pre	78.47 ± 8.19	79.57 ± 9.89	−1.10	−5.14	2.94	.590	.464
	Post	77.80 ± 5.70	79.72 ± 8.79	−1.92	−5.22	1.37	.249	
	Change	−0.67 ± 4.7	0.15 ± 6.35	−0.82	−3.31	1.66	.512	

[a]Intervention minus control group.
[b]Paired sample Student *t* test.
[c]Obtained from ANCONA test, adjusted for age, BMI, energy intake, physical activity, and baseline measures.

The present study has several limitations which should be taken into account while interpreting the finding. First, the duration of the study was relatively short that might be not sufficient for achieving an optimal result, but we could reveal the potential therapeutic effect of garlic on lipid parameters event in this duration. To determine the magnitude of garlic supplementation more studies with longer duration are needed. Second, the sample size assessed based on the difference in TG levels which might be not enough to achieve significant change in other outcomes. Finally, while we tried to diminish the impact of some confounders such as diet and physical activity by controlling them during the study as well as adjusting for potential factors, there are still other confounders that might affect the results.

5 | CONCLUSION

The present study suggested that garlic supplementation with 800 mg/d dosages for 8 weeks might improve TC and LDL-C and also might be effective on SBP and TG among PCOS patients. The garlic is generally safe and could be considered as an adjuvant therapy along with conventional treatment. This study provides some promising findings; however, it was not clinically significant and further studies are necessary to confirm its properties in clinical treatment.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

Roya Zadhoush, Amirmansour Alavi-Naeini, and Awat Feizi: Contributed to the conception and design of the research. **Roya Zadhoush, Mohammad Reza Ghazvini and Elham Naghshineh:** Contributed to the acquisition and analysis of the data. **Roya Zadhoush:** Drafted the initial manuscript. All authors critically revised the manuscript, agree to be fully accountable for ensuring the integrity and accuracy of the work, and read and approved the final manuscript.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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