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Effect of *Nigella sativa-L* supplementation on glycemia in adolescent polycystic ovarian syndrome: secondary analysis of a randomized controlled trial study

Azamsadat Mahmoudian[1], Akram Ashouri[2], Fatemeh Mohammadzadeh[3], Roghaieh Rahmani Bilandi[4], Sareh Dashti[5,6] and Narjes Bahri[2*]

Abstract

Introduction Adolescence is a critical period for health, as conditions like polycystic ovarian syndrome (PCOS) can affect long-term outcomes, including diabetes and other non-communicable diseases in adulthood. This study evaluated the effects of *Nigella sativa* L. extract on glycemia among adolescents with PCOS.

Materials and methods This secondary analysis used data from a randomized controlled trial conducted between March 2022 and March 2023. One hundred sixteen adolescent girls aged 12–18 years with PCOS were randomized into two groups. The intervention group received 1000 mg/day of *Nigella sativa* extract for 16 weeks, while the control group received 10 mg/day of medroxyprogesterone for 10 days per menstrual cycle over the same period. Fasting plasma glucose (FPG) and one- and two-hour post-prandial glucose levels were measured at baseline and after the intervention.

Results 103 completed the study (50 in the *Nigella sativa* group and 53 in the control group). At baseline, there were no significant differences in FPG ($p=0.294$), though the control group had higher one-hour ($p=0.002$) and two-hour ($p=0.006$) post-prandial glucose levels. Post-intervention, significant interaction effects were observed for FPG ($p=0.004$) and two-hour post-prandial glucose ($p=0.023$), indicating more significant reductions in the *Nigella sativa* group compared to the control group.

Conclusions Considering the observed effect of *Nigella sativa* supplementation on FPG and two-hour post-prandial glucose, it may offer a complementary approach to managing glycemia in adolescent PCOS. However, further research is warranted.

Keywords Polycystic ovary syndrome, Adolescent, Nigella sativa, Blood glucose metabolism

*Correspondence:
Narjes Bahri
nargesbahri@yahoo.com

Full list of author information is available at the end of the article

Introduction

The World Health Organization defines adolescence as 10 to 19 years old [1]. Adolescence is a critical period of life due to growth, development, and puberty [2]. Adolescent health is essential since disturbances during this period might affect health later in life. For instance, nearly 25% of the adult bone mass is acquired during adolescence [3]. It was previously reported that obesity during adolescence can increase the risk of type 2 diabetes and mortality due to cancer in adulthood [4, 5]. A study on 2798 adolescents reported that obesity and metabolic syndrome in adolescence were associated with an increased risk of type 2 diabetes after 11.3 years of follow-up [6]. The study also reported a higher risk for diabetes in later life among girls with metabolic syndrome compared to boys [6]. Another health issue that can arise from adolescence is polycystic ovarian syndrome (PCOS) [7]. Adolescence PCOS is found to be associated with type 2 diabetes, obesity, infertility, and some types of cancers in adulthood [8–10].

PCOS is defined as the presence of two of the following criteria: (1) polycystic ovaries in ultrasound scan, (2) irregular menstruation, and (3) hyperandrogenism [11]. PCOS is among the most common conditions in women of reproductive age, with a global prevalence ranging from 9.2 to 11.5% based on the diagnostic criteria used [12]. The prevalence of PCOS based on different diagnostic criteria has been reported to range between 6 and 18% during the adolescence period [7]. The etiology of PCOS is not fully understood, but one of the hypothetical etiologies is insulin resistance [13]. Therefore, insulin sensitizers have been used to treat PCOS [13, 14]. It should be noted that the diagnosis of PCOS during adolescence is not as straightforward as in adulthood since the presence of irregular menses, acne, and ovarian polycystic morphology might be neglected and misclassified as physiological changes due to puberty [15].

Specific criteria have been suggested for the components of PCOS in adolescence. For instance, ovulation dysfunction can be identified by the menstruation interval (more than 90 days in the first year of menstruation or less than 21 or more than 45 days consecutively for two or more years after menstruation) and no sign of menstruation by the age of 15 or absence of menstruation two to three years after thelarche [16]. Hyperandrogenism can be identified as moderate to severe hirsutism, the presence of refractory acne, and elevated serum total and free testosterone [16]. The goals of PCOS treatment in adolescence include improving the quality of life and reducing or preventing the progression of hyperandrogenism and ovulation dysfunction [17]. Lifestyle modification is the main compartment of PCOS management in adolescence and focuses on weight loss in obese individuals, preventing or reducing insulin resistance, and improving the quality of life. Medications include oral contraceptives, insulin sensitizers, and dietary supplements [13]. Complementary and alternative medicine has also been suggested in the management of PCOS [18].

Adolescents have been reported to have poor glycemic control due to their low level of adherence to medications due to psychological issues in the adolescent period, lack of parental supervision, and poor self-control [19, 20]. Considering the challenges in managing glycemia in adolescents, herbal and complementary medicine could aid in achieving the desired glucose serum level [21–23]. Some herbal medicines effectively manage insulin resistance in PCOS [24]. Black seed (*Nigella sativa Linn*) has been used as a traditional medicine in India, Europe, and the Middle East [25]. Among the therapeutic potentials of black seed is its anti-diabetic properties through various mechanisms, including improvement of insulin resistance, upregulating glucose-like growth factor 1, and increasing insulin signaling [26]. As glycemic control is one of the goals of PCOS treatment, it is hypothesized that Nigella sativa L. can be effective in reducing insulin resistance in adolescents with PCOS.

To the best of our knowledge, few studies have evaluated the administration of *Nigella sativa L* to manage PCOS in adolescence, and the studies that have been carried out on adolescent patients evaluated the effect of *Nigella sativa L* on ovarian size and PCOS criteria without investigating its possible mechanism of action [27, 28]. Therefore, it was hypothesized that *Nigella sativa* supplementation will improve glycemic control in adolescent PCOS patients. This study aimed to evaluate the effect of *Nigella sativa L*. supplementation on glycemia in adolescents with PCOS by looking into the data of a randomized controlled trial.

Method

Study design

This study is a secondary analysis of data obtained from a previously published randomized controlled trial conducted between March 2022 and March 2023 [27]. The trial was approved by the Ethical Committee of the Gonabad University of Medical Sciences (IR.GMU.REC.1401.080) and registered in the Iran Registry of Clinical Trials (IRCT20221017056209N1). Details of the original trial design, including sample size calculations and recruitment procedures, have been previously described [27]. Considering the financial limitations, the availability of serum samples from the mentioned study, and the adequate sample size, this study was conducted based on the laboratory tests from the previously mentioned study.

Study participants

Adolescent girls aged 12–18 years diagnosed with polycystic ovary syndrome (PCOS) based on the Amsterdam criteria for adolescents (requiring all three Rotterdam criteria) were included in the original trial. Participants were recruited via convenience sampling from patients referred to Obstetrics and Gynecology Clinics affiliated with the Gonabad University of Medical Sciences. The primary publication describes key inclusion and exclusion criteria and the detailed recruitment process [27]. For this secondary analysis, the dataset included 50 participants in the intervention (Nigella sativa) and 53 in the control (medroxyprogesterone) groups.

Blinding and randomization

Randomization and blinding procedures followed the original trial protocol. Participants were randomized into two groups using permutated block allocation, and randomization details are fully outlined in the primary study [21]. Due to differences in intervention, blinding was not feasible [27].

Interventions

As described in the primary study [21], the intervention group received 1000 mg Nigella sativa L. extract capsules daily for 16 weeks, while the control group received 10 mg medroxyprogesterone tablets for 10 days per month starting from the 14th day of the menstrual cycle. The dosing was based on a previous study [29]. As this study was a secondary analysis of an RCT on adolescents with PCOS, the control group only received hormonal medication for PCOS management based on the treatment protocol of the clinics. Weekly SMS reminders were sent to encourage adherence, and participants maintained a logbook to record medication usage.

Measurements

This secondary analysis focuses on glycemic indices, specifically fasting plasma glucose (FPG) and one- and two-hour post-prandial plasma glucose levels. These indices were measured at baseline and the end of the 16-week intervention using venous blood samples analyzed by a biochemical analyzer (Mindray BS600 automatic analyzer, Japan). FPG was measured after overnight fasting. Demographic, anthropometric, and other clinical measurements, including ovarian volume and Ferriman-Gallwey scoring, were also assessed in the original study but are outside the scope of this analysis. Complete measurement protocols have been reported previously [21].

Study procedure

Through face-to-face interviews, eligible participants were identified and screened based on inclusion and exclusion criteria. Informed consent was obtained from their parents or guardians, and baseline assessments of ovarian size, hormonal status, anthropometry, and glycemic indices (FPG and plasma glucose one and two hours post-prandial) were performed as stated in the previous article [27]. Participants were randomly assigned using sealed envelopes containing allocation codes. Weekly reminders via SMS were sent to ensure adherence to the medication regimen. The participants in both groups were asked to record their medication usage. Post-intervention evaluations were conducted at 16 weeks for all participants.

Statistical analysis

The Kolmogorov-Smirnov test was employed to evaluate the normality of continuous variables. As all variables—including age, age at menarche, birth order, number of siblings, and duration of PCOS diagnosis—were determined to be non-normally distributed, descriptive statistics are presented as median (interquartile range [IQR]). Categorical variables were summarized as frequencies (percentages). Between-group comparisons were performed using the Mann-Whitney U test for continuous variables.

For this secondary analysis, linear regression models were used to evaluate the effects of treatment, time, and their interaction on glycemic indices. An interaction term was created by multiplying the two variables (time and treatment) included in the model and the main effects of time and treatment. The assumptions of the linear hierarchical models—including normality, homoscedasticity of variance, and residuals' independence were evaluated. Normality was assessed using the Kolmogorov-Smirnov test and skewness and kurtosis values. Homoscedasticity was examined through plots of standardized residuals against predicted values, and the independence of residuals was verified using a residual time series plot. Statistical significance was set at $p < 0.05$. The Statistical Package for Social Sciences (SPSS) version 21 (IBM SPSS Statistics) was used to perform the statistical analyses.

Results

Out of the initial 116 adolescent girls with PCOS who met the eligibility criteria, 58 were allocated to the intervention group receiving Nigella sativa supplementation and 58 to the control group. During the study, 8 participants in the Nigella sativa group were excluded due to lack of adherence to the medication protocol and refusal to participate. Similarly, 5 participants in the control group were excluded due to refusal to participate. As a result, the final analysis included 50 participants in the Nigella sativa group and 53 participants in the control group (Fig. 1).

The baseline characteristics showed no significant differences between the groups (Fig. 2). Specifically, the

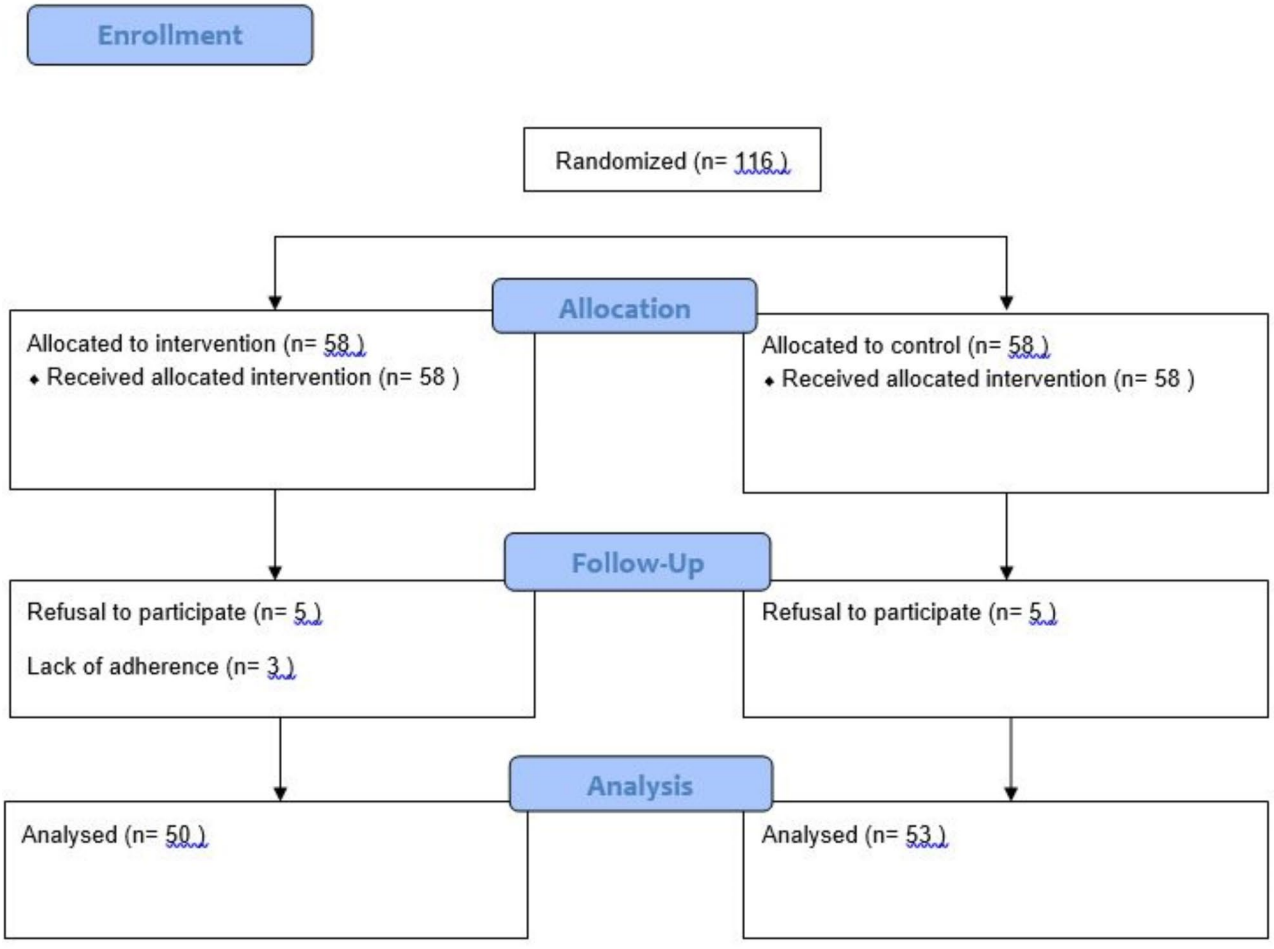

Fig. 1 Flow chart of the study

median age and interquartile range (IQR) were similar for the *Nigella sativa* group (17, 16–18 years) and the control group (17, 16–18 years) ($p = 0.418$) (Fig. 2). The median duration of PCOS diagnosis was 6 years (IQR: 4–7) in the "Nigella sativa" group and 5 years (IQR: 4–7) in the control group, with no significant differences between the two groups ($p = 0.184$). Additionally, there were no significant differences in median age at menarche ($p = 0.555$), birth order ($p = 0.265$), and number of siblings($p = 0.386$) between the groups (Fig. 2).

Comparison of the glycemia indices between Nigella sativa and control groups

Fasting plasma glucose (FPG)

Before the intervention, the mean fasting plasma glucose (FPG) was 84.52 mg/dL (SD = 13.72) in the Nigella sativa group and 87.26 mg/dL (SD = 9.75) in the control group. The regression results showed that the group effect was insignificant ($p = 0.294$p = 0.294p = 0.294), indicating no statistically significant difference in baseline FPG levels between the Nigella sativa and control groups. After the intervention, the FPG decreased to 76.92 mg/dL (SD = 9.37) in the Nigella sativa group and increased to 86.73 mg/dL (SD = 9.52) in the control group.

The time effect was not statistically significant ($p = 0.095$), suggesting that the reduction in FPG from before to after the intervention within the Nigella sativa group was not strong enough to be considered statistically meaningful. However, the interaction effect between time and group ($p = 0.004$) was significant, indicating that the change in FPG levels over time differed significantly between the two groups. This significant interaction suggests that the control group experienced an increase in FPG after the intervention. In contrast, the Nigella sativa group experienced a reduction, leading to a statistically significant difference in the trajectory of changes between the two groups (Table 1).

Plasma glucose 1-hour post-prandial

At baseline, the mean one-hour post-prandial glucose level was 99.02 mg/dL (SD = 13.66) in the Nigella sativa group and 107.91 mg/dL (SD = 15.83) in the control

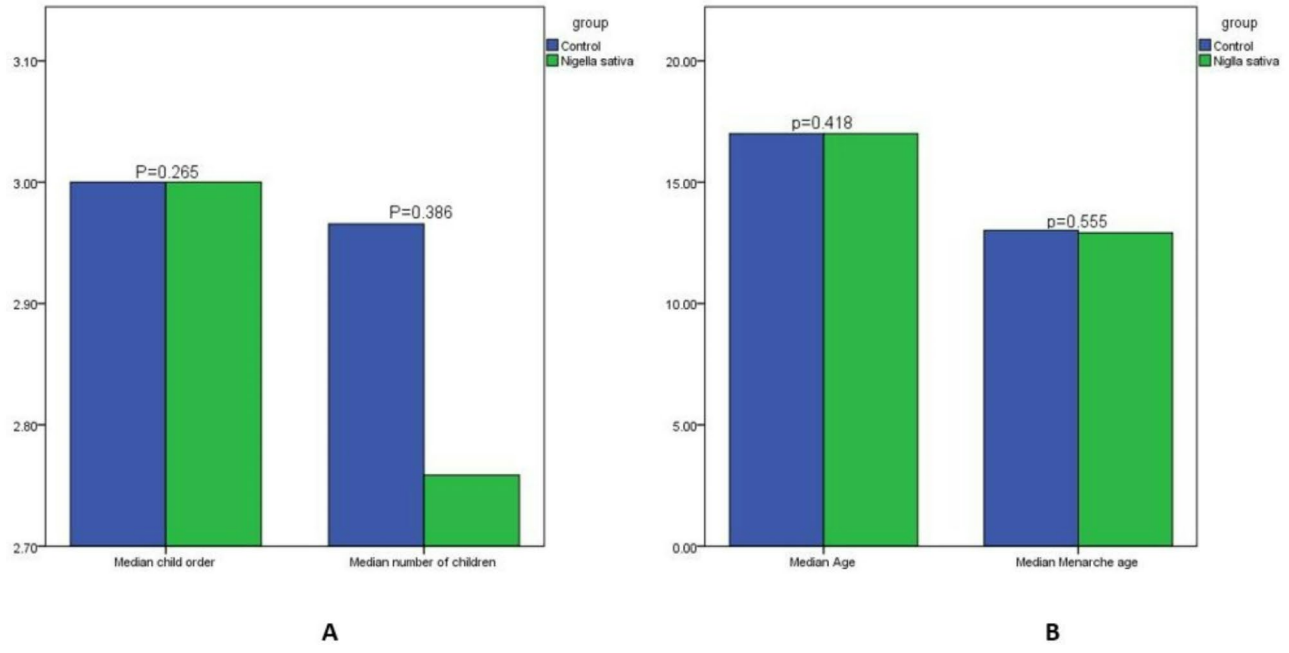

Fig. 2 Comparison of the median birth order and number of siblings(**A**) and median age and menarche age (**B**) between Nigella sativa and control groups

Table 1 Comparison of the glycemia indices between Nigella sativa and control groups

Dependent variable	Measurement time	Group		*Linear regression results*				
		Intervention (Nigella sativa)	Control (Medroxyprogesterone)	Effect	B	Std. Error	t	*p*
		Mean (S.D.)	Mean (S.D.)					
FPG (mg/dL)	Before	84.52 (13.72)	87.26 (9.75)	Time	7.86	4.68	1.68	0.095
				Group	-2.13	2.03	-1.05	0.294
	After	76.92 (9.37)	86.73 (9.52)	Time*group	-8.44	2.92	-2.90	0.004
Plasma glucose 1 h post-prandial (mg/dL)	Before	99.02 (13.66)	107.91 (15.83)	Time	0.02	0.02	0.92	0.357
				Group	-0.03	0.01	-3.16	0.002
	After	94.04 (11.22)	103.60 (16.54)	Time*group	-0.02	0.02	-1.58	0.116
Plasma glucose 2 h post-prandial (mg/dL)	Before	92.26 (11.83)	98.57 (6.89)	Time	0.03	0.02	1.59	0113
				Group	-0.03	0.01	-2.83	0.006
	After	87.16 (11.55)	98.49 (8.49)	Time*group	-0.03	0.01	-2.30	0.023

Notes: FPG, Fasting plasma glucose, Regression coefficient; SD, Standard Deviation; Std. Error, Standard Error

group. The regression results showed a significant group effect ($p = 0.002$), indicating that the control group had significantly higher one-hour post-prandial glucose levels at baseline compared to the Nigella sativa group.

After the intervention, the one-hour post-prandial glucose decreased to 94.04 mg/dL (SD = 11.22) in the Nigella sativa group and 103.60 mg/dL (SD = 16.54) in the control group. The time effect was not statistically significant ($p = 0.357$), meaning that the reduction in one-hour post-prandial glucose within the Nigella sativa group alone was not meaningful. Additionally, the interaction effect between time and group was also not significant ($p = 0.116$), indicating no statistically significant difference in the changes over time between the two groups. These findings suggest that while the Nigella sativa group had lower glucose levels overall, the intervention did not lead to significantly different patterns of change in one-hour post-prandial glucose compared to the control group (Table 1).

Plasma glucose 2-hour post-prandial

Before the intervention, the mean two-hour post-prandial glucose level was 92.26 mg/dL (SD = 11.83) in the Nigella sativa group and 98.57 mg/dL (SD = 6.89) in the control group. The regression results showed a significant group effect ($p = 0.006$), indicating that the control group had significantly higher two-hour post-prandial glucose levels at baseline compared to the Nigella sativa group.

After the intervention, the two-hour post-prandial glucose decreased to 87.16 mg/dL (SD = 11.55) in the

Nigella sativa group and 98.49 mg/dL (SD = 8.49) in the control group. The time effect was not significant ($p = 0.113$), meaning that the reduction in two-hour post-prandial glucose within the Nigella sativa group was not statistically strong. However, the interaction effect was significant ($p = 0.023$), indicating that the two-hour post-prandial glucose levels over time differed significantly between the groups. This suggests that while the Nigella sativa group experienced a greater reduction, the control group's glucose levels remained relatively stable, leading to a significant difference in the trajectories of change (Table 1).

Discussion

This secondary analysis of the RCT indicated that *Nigella sativa L.* extract supplementation with 100 mg/d for 16 weeks improved glycemia in adolescent girls with PCOS regarding FPG and plasma glucose two hours post-prandial, as evidenced by the significant interaction of time and group.

This study's findings regarding the effects of *Nigella sativa L.* extract on FPG and plasma glucose two hours post-prandial were in line with previous preclinical studies on animal models of PCOS [30, 31]. Thymoquinone is believed to be the main component of Nigella sativa L. that affects PCOS status and insulin resistance [26]. In an animal study, thymoquinone administration to rat models of PCOS resulted in improved glycemia and other markers of PCOS [30]. This effect has been associated with thymoquinone's anti-inflammatory and insulin receptor-upregulating properties [26, 32]. However, human studies show contradictory results. For instance, the survey by Ammar et al. (2021) on 207 overweight or obese adult PCOS women showed that although 6 months of thymoquinone supplementation (1500 mg/d) along with metformin administration improved oxidative stress and PCOS symptoms and glucose tolerance compared to the control group who only used metformin [33]. Another study also showed that a 16-week Nigella sativa extract supplementation (100 mg/d) did not improve glycemia [29]. Similarly, in another study on 62 newly diagnosed diabetic patients, Nigella sativa did not improve glycemia compared to metformin [34]. The reason for the difference in the findings of previous studies and current studies' findings might be related to the treatment in the control group.

In contrast, the control group received medroxyprogesterone, and the mentioned studies administered metformin, which has anti-diabetic effects [29, 33, 34]. Furthermore, the difference in findings between animal and human studies might be related to the experimental settings of the studies. Animal studies are controlled experiments, but human studies may not be as easily controlled due to various confounders and ethical considerations. Therefore, although the mechanism of effect in both study types might be similar, the strength of the impact might be different.

This study found no significant time effect for FPG and post-prandial glucose, indicating that the reduction in these levels within the Nigella sativa group before and after the intervention was not statistically meaningful. This finding might be related to the fact that none of the adolescents in this study were diagnosed with overt hyperglycemia or diabetes. Since the glucose level in most participants was within the normal range, the lack of a significant time effect could be justified in this study.

The hypoglycemic effects of Nigella sativa have been reported in previous studies on healthy individuals [35] and patients with type 2 diabetes [36]. These findings are further reinforced by a recent survey by Alamdar et al. on 48 overweight women; 1000 mg/d Nigella sativa supplementation with or without high-intensity training improved FPG [37]. These studies' findings align with the current study's results, which also observed the hypoglycemic effects of Nigella sativa L. extract. Notably, as no hypoglycemic medications were included in either group, the observed glucose-lowering effects can be attributed to Nigella sativa. Overall, the current study's findings regarding the impact of Nigella sativa L. extract supplementation on anthropometric parameters, ovarian size, and glucose tolerance, It could be hypothesized that the effect of Nigella sativa L. on PCOS might be through the improvement in insulin resistance.

One of the limitations of the current study was the lack of data on the insulin level of the participants since the current study was conducted on the recorded data in a previous RCT with a different objective. Therefore, it is suggested that further studies evaluate the effect of Nigella sativa L. extract supplementation on insulin resistance, considering laboratory parameters including fasting and post-prandial insulin. Future research should involve more extensive, more diverse populations across multiple clinical centers to improve the generalizability of findings. Since this study was considered an early phase II clinical trial and blinding was not performed to identify possible adverse effects by the caregivers and physicians, lack of binding could have affected the study's outcome. Therefore, it is suggested that further studies evaluate the effects of Nigella Sativa on glycemia in adolescents with PCOS using blinding. Although these findings were observed in 6 weeks, the long-term effects and the duration of the effects of the Nigella Sativa supplementation were not evaluated in this study. Therefore, future studies with longer follow-up duration are necessary.

The overall findings of the current study indicated the possibility of the administration of *Nigell sativa L.* supplement besides PCOS treatment in adolescents to improve glycaemia and treatment outcomes.

Conclusion

The current study showed that *Nigella sativa L.* extract supplementation for 16 weeks improved the anthropometric and glycemic status of adolescent girls with PCOS. These findings indicated that the possible mechanism of this effect might be enhanced insulin resistance due to Nigella sativa L. supplementation. Therefore, including Nigella sativa L. supplementation in the conventional medical treatment of adolescent PCOS may be beneficial and improve the medications' effects. However, this hypothesis needs to be further evaluated regarding long-term outcomes and the mechanism of action of Nigella sativa L.

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Author contributions
Study concept and design: A. A., and N. B.; analysis and interpretation of data: F. M., and S. D.; drafting of the manuscript: A. M., and R. R.; critical revision of the manuscript for important intellectual content: N. B., S. D., and F. M. statistical analysis: F.M.

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Data availability
The datasets generated and analysed during the current study are not publicly available due but are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
The Gonabad University of Medical Sciences Ethics Committee approved this study (Code: IR.GMU.REC.1401.080). The study was registered in the Iran Registry of Clinical Trials (registration code: RCT20221017056209N1). All participants and their parents or guardians provided written informed consent at the time of participation in the study and were free to leave the study at any time.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Author details
[1]Department of Obstetrics & Gynecology, School of Medicine, Reproductive Health and Population Research Center, Gonabad University of Medical Sciences, Gonabad, Iran
[2]Department of Midwifery, School of Medicine, Social Determinants of Health Research Center, Gonabad University of Medical Sciences, Gonabad, Iran
[3]Department of Epidemiology and Biostatistics, School of Health, Social Development & Health Promotion Research Center, Gonabad University of Medical Sciences, Gonabad, Iran
[4]Department of Midwifery, Faculty of Medicine, Reproductive Health and Population Research Center, Gonabad University of Medical Sciences, Gonabad, Iran
[5]Department of Midwifery, Faculty of Nursing and Midwifery, Mashhad Medical Sciences, Islamic Azad University, Mashhad, Iran
[6]Department of Public Health, Faculty of Paramedicine, Mashhad Medical Sciences, Islamic Azad University, Mashhad, Iran

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