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Exploring the therapeutic impact of *Salvia officinalis* on lipid and oxidative stress markers in patients with polycystic ovary syndrome – a randomized placebo-controlled clinical trial

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Abstract

Background *Salvia.officinalis* (*S. officinalis*), is recognized for its antihyperlipidemic, metabolism-regulating, and antioxidant properties in diabetic and hyperlipidemic disorders. This study examining its effects on lipid and oxidative stress (OS) markers in patients with Polycystic Ovary Syndrome (PCOS), thereby substantiating its role in managing metabolic disorders.

Methods In this randomized placebo-controlled trial was performed in gynecology clinics affiliated to Iran University of Medical Sciences. Accordingly, 70 Iranian married women aged 15–40 years with newly diagnosed PCOS were included. They were randomized to receive either 330 mg of *S. officinalis* extract or placebo daily for eight weeks. The study outcomes included lipid profile and OS markers.

Results The study found a significantly lower triglyceride levels and malondialdehyde after eight weeks of *S. officinalis* extract intake compared to placebo. Also, the mean change of triglyceride, high-density lipoprotein cholesterol, malondialdehyde, and total antioxidant capacity were statistically significant in intervention group.

Conclusion The study demonstrates that *S. officinalis* extract can significantly reduce triglyceride levels and OS in patients with PCOS, suggesting its potential as an adjunctive natural therapy for managing metabolic and oxidative imbalances associated with this condition. While the extract did not significantly alter other lipid profile markers, the observed improvements highlight the therapeutic promise of *S. officinalis*. These findings support further investigation into the clinical applications *S. officinalis* for PCOS and its potential benefits for metabolic health.

Trial registration IRCT201504146917N2 on 2015–10-03 (registered while recruiting).

Keywords Polycystic ovary syndrome, Metabolism lipid profile, Oxidative stress salvia officinalis, Lamiaceae family, Common sage

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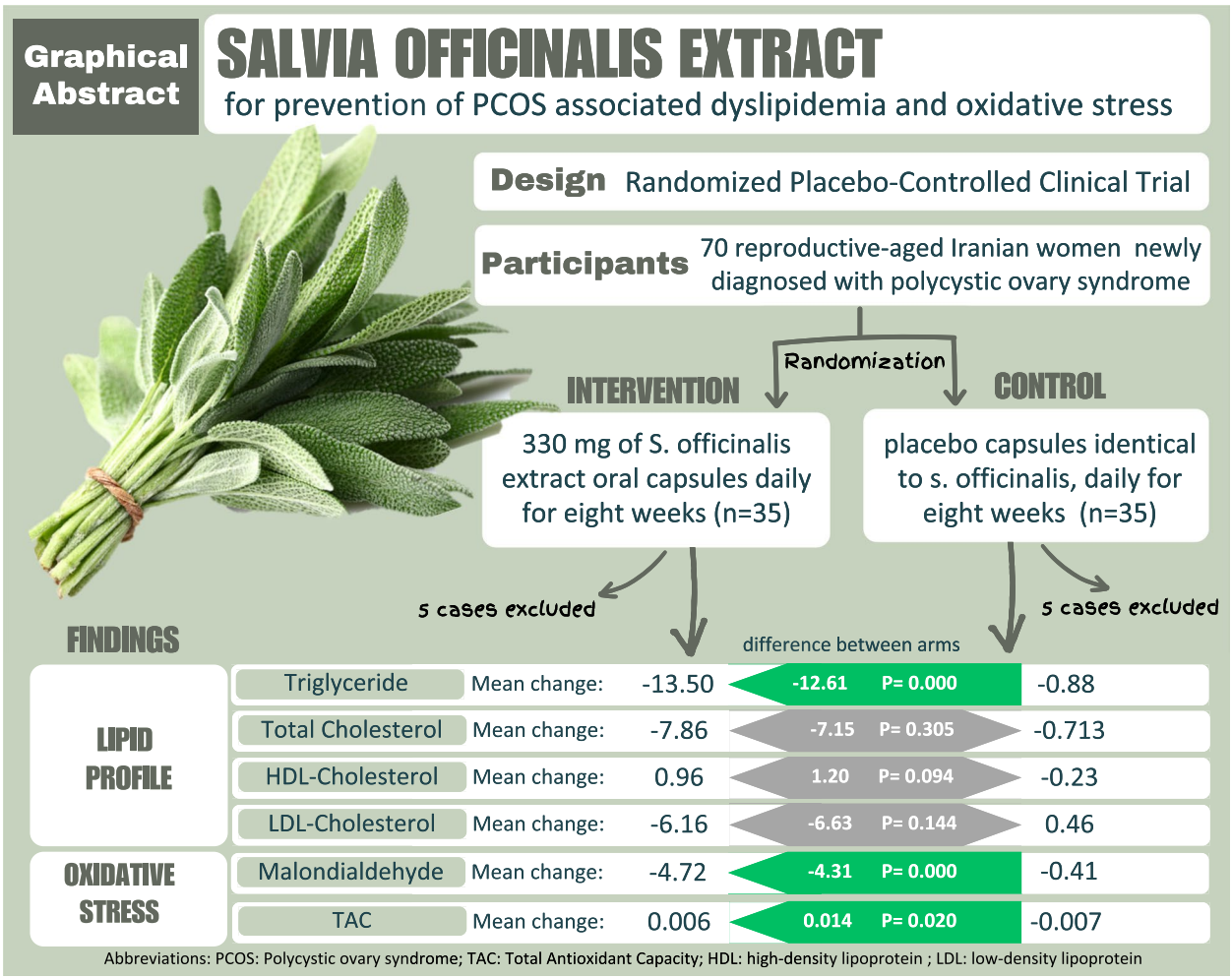
Graphical Abstract



Introduction

Polycystic ovary syndrome (PCOS) is a multifaceted endocrinopathy in women of reproductive age with is associated with various hormonal disturbances and metabolic complications like ovarian dysfunctions, infertility, metabolic syndrome, dyslipidemia, and cardiovascular disease [1, 2]. Several studies revealed that there is a complex interaction between oxidative stress (OS) and PCOS-induced metabolic disorders including obesity, diabetes mellitus, dyslipidemia, and cardiovascular disease [3, 4]. Elevated OS levels can exacerbate insulin resistance, inflammation, and apoptotic events in ovarian cells. Furthermore, it is well-documented that metabolic dysfunctions such as insulin resistance and dyslipidemia contribute to systemic OS and an overproduction of reactive oxygen species, creating a vicious cycle that amplifies both metabolic disturbances and OS [5]. Among the PCOS-associated metabolic abnormalities, dyslipidemia is one of the most common findings, regardless of body mass index or ethnicity [6, 7]. Lipid metabolism abnormalities contribute to the increased risk of cardiovascular diseases in PCOS patients. Also, dyslipidemia promotes the development of insulin resistance, hyperandrogenism, OS, and anovulation in PCOS [8]. Additionally, in PCOS patients with dyslipidemia reproductive outcomes such as embryo quality, oocyte maturation, and endometrial receptivity are compromised, even in lean patients [9, 10]. Apart from metabolic complications, OS can induce a chain of inflammatory reactions, which subsequently impairs oocyte developmental competence and reproductive outcomes in women with PCOS [11, 12].

Given the intricate pathogenesis of PCOS and the absence of a universally safe and targeted therapeutic approach to mitigate the associated metabolic and cellular detriments, there has been an increasing inclination in recent years toward the adoption of complementary and herbal medicinal modalities [13, 14]. *Salvia officinalis* L. *(S. officinalis)* or Common Sage from the Lamiaceae family, with over 900 species worldwide and about 60 species in Iran, has been used to treat various diseases due to its potential medicinal properties [15–22]. The phytochemical investigations of *S. officinalis* reveal metabolites such as carnosic acid, rosmarinic acid, diterpenoids, triterpenoids, flavonoids, polyphenols, and phenolic glycosides, which contribute to its antidiabetic, antioxidant, antimicrobial, cytotoxic, and anti-inflammatory effects [15, 23–25].

S. officinalis poses potential inhibitory effects on key digestive enzymes such as α-Glucosidase, α-amylase, and pancreatic lipase, which play a role in managing diabetes and hyperlipidemia, conditions often associated with PCOS [26, 27]. By acting as an agonist to peroxisome proliferator-activated receptor γ (PPARγ), *S. officinalis* may improve the HDL/LDL ratio and reduce adipose tissue, offering dual benefits in PCOS management by enhancing glycemic control and lipid metabolism regulation [15, 16, 28–30].

The hypolipidemic effects of *S. officinalis* have been confirmed in various models of metabolic disorders. For instance, *S. officinalis* essential oil demonstrated effects similar to simvastatin, including reducing body weight gain, lipid levels, and OS in mice [31]. *S. officinalis* aqueous extract also has normalized metabolic markers in obese rats [32]. Human studies, including clinical trials and systematic reviews, have also indicated improvements in lipid profiles, glycemic control, and antioxidant defenses with *S. officinalis* supplementation [16, 28, 33–36]. These findings suggest a promising role for *S. officinalis* in managing dyslipidemia and diabetes. Besides *S. officinalis*'s promising effects on metabolic diseases like diabetes, its positive impact has been documented in different reproductive disorders; however, most of these studies focused only on reproductive abnormalities like ovarian function [37–39] or metabolic disturbances related to diseases other than PCOS, like menopause or ovariectomy [40–43]. *S. officinalis*'s effectiveness in addressing PCOS-related metabolic disturbances has been less extensively studied, with only one animal model demonstrating its efficacy [44]. This study highlighted the therapeutic potential of *S. officinalis* tea in rats with testosterone-induced PCOS, showing increased antioxidant capacity and improved lipid profiles, suggesting cardiovascular benefits for PCOS patients. In our previous manuscript, we found that *S. officinalis* extract helped in glycemic control and preventing insulin resistance in euglycemic PCOS patients [45]. Building upon our previous findings, this report delves into additional outcomes of the same trial, particularly focusing on lipid profile indices and OS markers. These outcomes offer further insights into the therapeutic potential of *S. officinalis*, shedding light on its broader implications for metabolic health in PCOS.

Materials and methods

As mentioned before, this manuscript is a report of additional outcomes of a parallel randomized placebo-controlled trial which some of its outcomes were published previously in another manuscript [45]. The trial was performed in gynecology clinics affiliated to Iran University Medical Scirences. We aimed to evaluate the efficacy of *S. officinalis* extract on the prevention of PCOS associated metabolic disturbances including obesity, hyperglycemia, insulin resistance, and hyperlipidemia and also OS. The details of the trial design, population, and intervention have been reported in the previous article, so we will briefly provide the trial protocol in the following sections.

Ethics statements

The study was designed and performed according to the Declaration of Helsinki and all participants signed an informed consent. Study protocol was approved by the Ethics Committee of Iran University of Medical Sciences (code of ethics is IR.IUMS.REC.1394.9211373221) and was registered in the Iranian registration of clinical trials (IRCT) website (https://irct.behdasht.gov.ir). The registration code is IRCT201504146917N2 and registration dateis 2015–10-03.

Participants

The trial enrolled Iranian married women aged 15–40 years women with newly diagnosed PCOS according to the Rotterdam Criteria. The Rotterdam Criteria requires the presence of two of the following: 1) oligomenorrhea or amenorrhea, 2) clinical (hirsutism) and/or biochemical signs of hyperandrogenism, and 3) polycystic ovaries in ultrasound [26]. Ferriman-Gallwey Score > = 8 defined as hirsutism [27]. Exclusion criteria were taking multivitamins, other herbal compounds, anti-hyperglycemic agents, or anti-hyperlipidemic agents; history of any medical or metabolic disorders; pregnancy or planning for pregnancy; and breastfeeding. Eligibility criteria were assessed and determined by an expert gynecologist.

Interventions

Seventeen eligible participants were randomly assigned in a 1:1 ratio to two parallel groups to receive either 330 mg oral *S. officinalis* extract (n:35) or placebo

capsules (n:35) daily for eight weeks. Details about sample size calculation was mentioned in previous manuscript [45].

Details of extraction were reported previously [45]. The Iranian native *S. officinalis* plants used in this study were sourced from the central herbal market in Tehran and verified by the pharmacognosy department at Shahid Beheshti University of Medical Sciences. This species is typically harvested from the Isfahan and northwest of Fars provinces, which are located adjacent to each other and share a semi-arid climate characterized by hot summers and mild to cold winters. This climate provides ideal conditions for the growth of *S. officinalis*, including well-drained soil and abundant sunshine, at elevations ranging from 1,500 to 1,600 m above sea level. The plants are usually harvested during the peak growing season to maximize the potency of their bioactive compounds.

The aerial parts of *S. officinalis* were ground using an electric grinder. The resulting powder was then combined with 96% ethanol in a process of maceration, repeated three times. Afterward, the extract was mixed with corn starch. We manually filled size 0 capsules with 330 mg of the powdered extract. For the placebo, the capsules were filled with corn starch only. The intervention group received capsules containing 330 mg of *S. officinalis* extract, while the placebo group received capsules filled solely with corn starch.

Participants were reminded to keep their physical activity and diet constant throughout the study and not to use any other herbal remedies, multivitamins, and antioxidants. To monitor the patients' compliance with the allocated treatments, a paper-based table was given to each participant for recording the daily intake of the assigned treatments. Also, the participants were checked for complications and compliance with the allocated treatment by a weekly phone call.

Randomization, blinding, and concealment

Simple randomization with a computer-generated random numbers table was used for treatment allocation. The randomization list was designed by study methodologist and its content was solely exposed to study methodologist. The subjects, outcome assessors, and the statistician were blinded about the type of interventions in each group. Accordingly, the capsules were identical in shape and packaging. A unique code was belonged to each participant according to the randomization list which was concealed from research staff by using sealed envelopes. Capsule containers were administered according to the codes provided in sealed envelopes. Study variables were also documented in anonymous coded forms.

Study outcomes

The study outcomes were changes in body mass index, waist to hip ratio, blood pressure, homoeostatic model assessment-insulin resistance (HOMA-IR), and quantitative insulin sensitivity check index (QUICKI), which were reported in previously published manuscript. The additional outcomes included in the present manuscript are the changes in lipid profile and OS markers. For this report of these outcomes, we used the same data source and sample as the previous article. We included all participants who completed the trial and had valid data for the lipid profile and OS outcomes.

The lipid profile included total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglycerides (TG), LDL to HDL ratio (LDL/HDL), TC to HDL-C ratio (TC/HDL-C) TG to HHDL-C ratio (TG/HDL-C). The OS markers included malondialdehyde (MDA) and total antioxidant capacity (TAC). These outcomes were measured at baseline and at the end of treatment.

Sample collection and preparation

Blood samples were collected from all participants after 12 h of fasting in the early morning. Blood samples were placed at room temperature for 20–30 min and then were centrifuged at 2500–3500 rpm for 10–15 min. The serum was isolated and stored at −80°C for later assessment.

Measurement of lipid profile

Serum levels of TC, TG, LDL-C, and HDL-C were measured by using Pars Azmoon company enzymatic kits (Tehran, Iran) and a Hitachi 912 autoanalyzer (Japan). Standard enzymatic method are widely accepted and validated for clinical and research purposes on lipid profile [46].

Measurement of OS markers

Serum levels of malondialdehyde (MDA) and total antioxidant capacity (TAC) were measured by colorimetry technique using commercial kits. We used ZellBio 48-piece and 96-piece kits (Germany) for MDA and TAC measurements. The sensitivity levels of the kits were 0.1 μM and 0.1 mM respectively. We performed the measurements according to the manufacturer's instructions and used a Hyperion MPR 4+microplate reader (USA) to read the absorbance at 535 nm for MDA and 490 nm for TAC. These tools provide standardized and validated methods for measuring OS markers [47, 48].

Statistical analyses

The data were analyzed using the same software and statistical methods as the previous article, with some

modifications. We used SPSS version 25 for data management and analysis. We checked the data for normality, outliers, and missing values. We used the intention-to-treat principle for the primary analysis. We used descriptive statistics to summarize the data, and independent t-tests to compare the baseline characteristics between the groups. We used paired t-tests to compare the changes in the outcomes within each group, and independent t-test to compare the changes in the outcomes between the groups. We used analysis of covariance (ANCOVA) to adjust for potential confounders, including bassline values of variable, age, BMI, and parity. We used a two-sided significance level of 0.05 for all tests.

Results

The baseline characteristics of the participants in this report (which are summarized in Table 1) and study flow diagram (Fig. 1) are the same as those reported in the previous article [45]. As illustrated in Fig. 1, a total of ten patients were excluded from the study, with five from the intervention group and five from the control group. Within the intervention group, the exclusion of one patient was attributed to gastrointestinal complications, which, upon medical evaluation, were determined to be unrelated to the intake of *S. officinalis*.

As reported previously, there were no significant differences between the *S. officinalis* and placebo groups at baseline and random allocation produced a balance between two arms regarding demographic, reproductive, and lifestyle variables.

Figures 2 and 3 summarized study findings on lipid profile and OS markers and Tables 2 and 3 present detailed data about the same outcomes. Among the lipid profile outcomes just TG (mg/dl) found a statistically significant difference compared with placebo after eight weeks of taking *S. officinalis* extract (MD = −17.25, 95% CI: −34.35 to −0.14; $P = 0.048$). TC (mg/d), HDL-C (mg/d), LDL-C (mg/d) and other ratios were identical between two groups after intervention. Also, results of linear mixed-effects models showed statistically significant differences between the two groups regarding mean change of TG ($P = 0.000$), HDL-C ($P = 0.047$), and TG/HDL-C ($P = 0.000$), adjusted for baseline value of dependent variable, age, and BMI, but there was no significant difference for other markers.

Consumption of *S. officinalis* extract, compared to the placebo, resulted in a significant decrease in MDA (μM) (MD: −3.44, 95%CI: −6.29 to −0.59, $P = 0.019$). TAC was also higher in intervention group compared to placebo at the end of intervention, but this difference was not statistically significant ($P = 0.080$). Results of linear mixed-effects models showed statistically significant differences between the two groups regarding mean change of MDA ($P = 0.000$) and TAC ($P = 0.024$).

Table 1 Patient's characteristic after random assignment

		Groups		*P*
		***S. officinalis* (*n* = 35)**	**Placebo (*n* = 35)**	
Age (years)	Mean ± SD	28.07 ± 4.18	29.23 ± 5.44	0.356†
	Median (range)	27.50 (22 to 38)	30 (17 to 39)	
BMI (Kg/m2)	Mean ± SD	25.55 ± 3.69	24.94 ± 3.35	0.504†
	Median (range)	24.84 (20.70 to 34.24)	24.43 (19.78 to 32.53)	
Gravidity	Mean ± SD	0.87 ± 1.22	1.03 ± 1.35	0.619†
	Median (range)	0 (0 to 5)	0 (0 to 4)	
Parity	Mean ± SD	0.67 ± 0.95	0.83 ± 1.08	0.619†
	Median (range)	0 (0 to 3)	0 (0 to 3)	
Infertility	Yes	2 (6.7%)	5 (16.7%)	0.696*
	No	28 (93.3%)	25 (83.3%)	
Oligomenorrhea	Yes	23 (76.7%)	17 (56.7%)	0.100*
	No	7 (23.3%)	13 (43.3%)	
Dysmenorrhea	Yes	5 (16.7%)	4 (13.3%)	0.718*
	No	25 (73.3%)	26 (86.7%)	
Ferriman–Gallwey Score	Mean ± SD	15.58 ± 4.78	14.50 ± 3.57	0.347†
	Median (range)	15.50 (8 to 23)	14 (8 to 22)	

The data presented in this table has been published previously in the manuscript of the same trial [45]

† Based on t-test

* Based on Chi-Square test

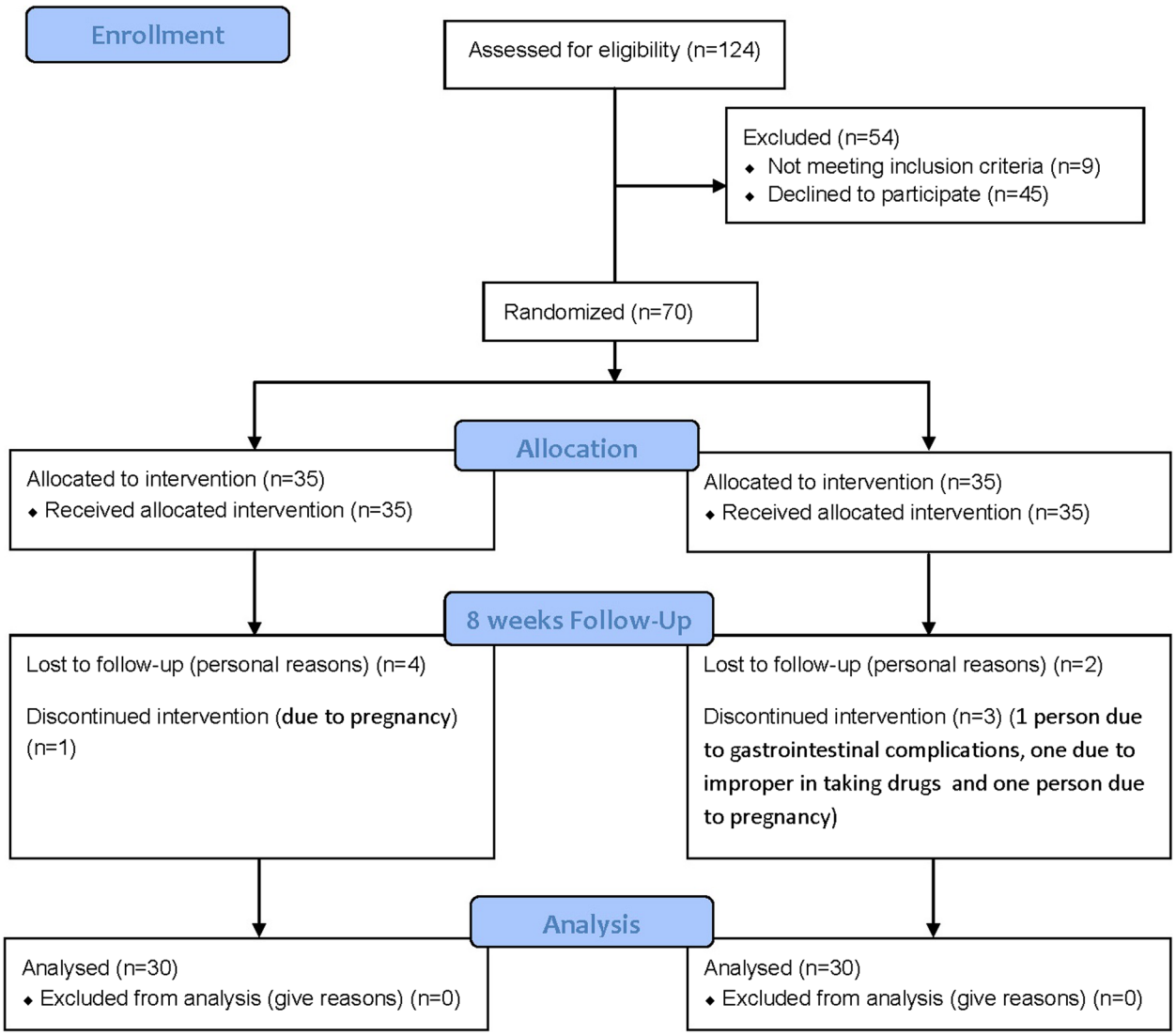


Fig. 1 Study flow diagram

Discussion

Summary of Study Findings

The findings from this study shed light on the effects of *S. officinalis* on lipid profiles and OS markers in patients with PCOS. The observed reduction in TG levels after an eight-week regimen of *S. officinalis* extract intake is particularly notable, suggesting its potential as a therapeutic agent for lipid metabolism regulation. This aligns with significant changes in TG, HDL-C, and the TG/HDL-C ratio, considering baseline values, age, and BMI. These results support the hypothesis that *S. officinalis* could be beneficial in managing and preventing dyslipidemia associated with PCOS, which is often linked to an increased risk of cardiovascular diseases. Additionally, the marked decrease in MDA and the increase in TAC suggest an antioxidative effect of *S. officinalis*. The interplay between lipid profile improvement and OS reduction could have significant implications for patients with PCOS-related metabolic disorders, where OS is known to exacerbate lipid abnormalities.

Justification of Study Findings and Comparison with Existing Literature

The therapeutic effects of *S. officinalis* are believed to be mediated through various bioactive compounds, like polyphenols and essential Oils. Polyphenolic compounds, such as rosmarinic acid, carnosic acid, and carnosol, have been shown to posse anti-inflammatory, antioxidant, and anti-hyperglycemic properties. These compounds may contribute to the improvement of lipid profiles and OS

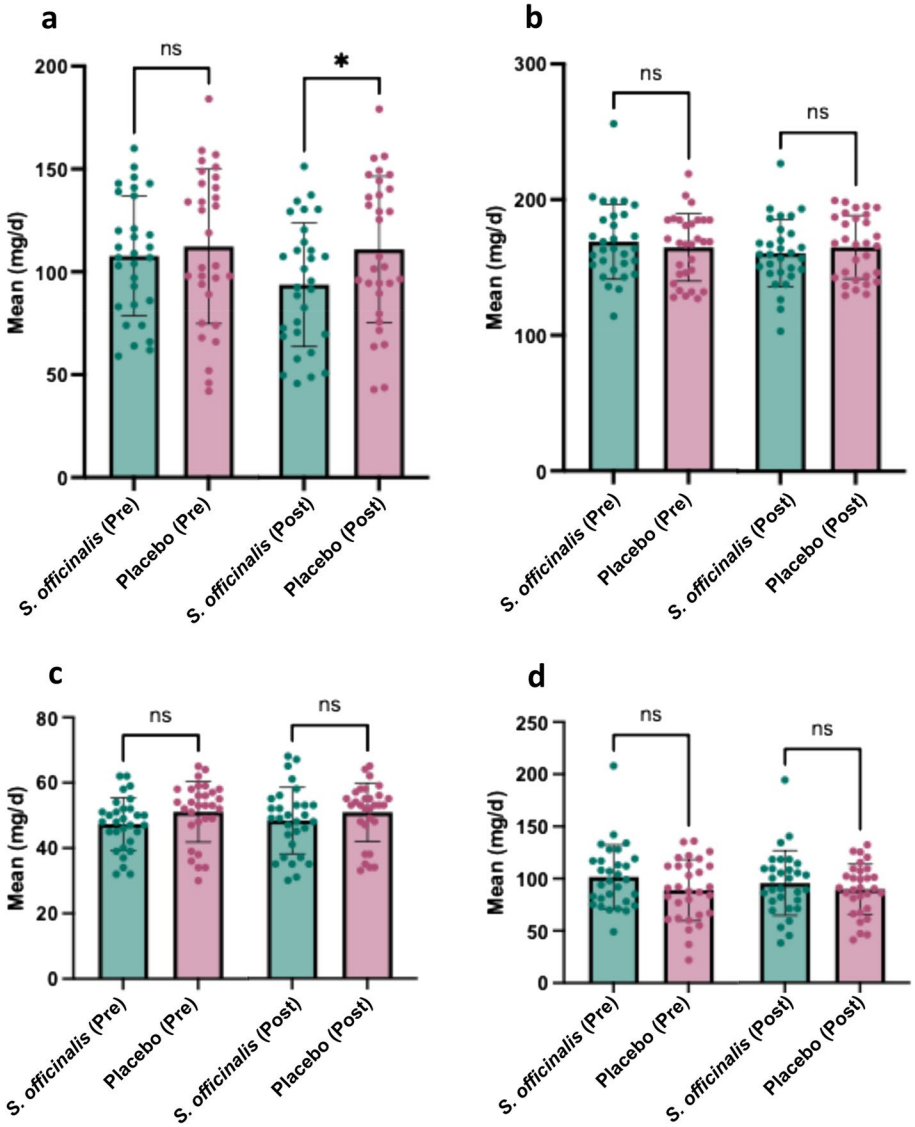


Fig. 2 A comparison of lipid profile parameters between the two groups before and after the intervention. **a** Triglyceride levels; **b** Total Cholesterol; **c** High-Density Lipoprotein Cholesterol; **d** Low-Density Lipoprotein Cholesterol. "ns" indicates non-significant results, while "*" signifies $P < 0.05$. Error bars represent standard deviation (SD), and each dot corresponds to data from one participant

markers by modulating enzymatic activities, gene expression, and signaling pathways involved in metabolism and inflammation [15, 23–25, 29, 30]. The essential oils of *S. officinalis*, including α-thujone, β-thujone, and camphor, have been reported to influence lipid metabolism [49]. This effect may be attributed to the ability of *S. officinalis* to suppress cholesterol biosynthesis. Thujone, in particular, has been shown to lower cholesterol and triglyceride levels by reducing their absorption or synthesis [28, 35]. Furthermore, *S. officinalis* poses potential inhibitory effects on key digestive enzymes such as pancreatic lipase [26, 27]. So, *S. officinalis* may influence lipid absorption in the intestines and lipid synthesis in the liver level. Some studies suggested that *S. officinalis* extracts can activate PPARγ, a nuclear receptor that plays a crucial role in regulating genes involved in lipid and glucose metabolism. By acting as a PPARγ agonist, *S. officinalis* can improve lipid clearance and reduce lipid synthesis. In addition to antihyperlipidemic activities, polyphenols from *S. officinalis* have potential antioxidative properties. By scavenging free radicals and reducing lipid peroxidation, sage can alleviate OS-associated cell damage and help maintain healthier lipid levels [50]. Meanwhile, further research into the specific mechanisms by which *S. officinalis* exerts

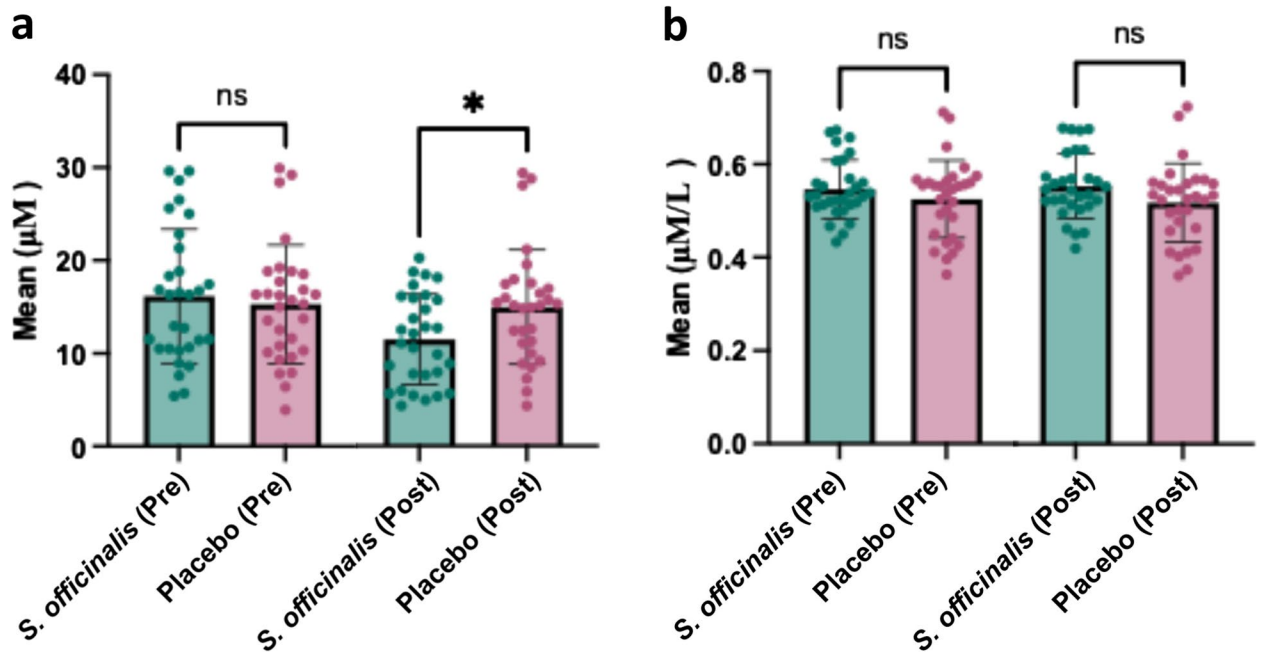


Fig. 3 A comparison of markers of oxidative stress between the two groups before and after the intervention. **a** Malondialdehyde; **b** Total Antioxidant Capacity. "ns" indicates non-significant results, while "*" signifies $P < 0.05$. Error bars represent standard deviation (SD), and each dot corresponds to data from one participant

its effects could provide deeper insights into its potential as a therapeutic agent for PCOS and related metabolic disorders.

The hypolipidemic activities observed in our study are consistent with other human clinical trials. The investigation by Carla M. Sa and colleagues [35] into the effects of *S. officinalis* tea on healthy women suggested improvements in lipid profile and antioxidant defense systems without impacting weight, blood pressure, or glycemic status. However, the limitations of their study, including its non-randomized design, small sample size, and short duration, suggest that higher doses or longer intervention periods might yield more significant metabolic improvements. Similarly, another study [34] observed reductions in two-hour postprandial blood sugar and total cholesterol following *S. officinalis* supplementation at a dose of 450 mg per day for three months in individuals with poorly controlled type 2 diabetes. Another randomized clinical trial [33] examined the impact of a higher dosage of *S. officinalis*'s alcoholic extract (three 500 mg tablets daily) on individuals with type 2 diabetes and hyperlipidemia over a three-month period, alongside standard diabetes treatments. The study concluded that this regimen significantly improved glycemic control and lipid levels. A previous study by the same team in 2011 [28] yielded comparable results when *S. officinalis* was used in conjunction with statin therapy in hypercholesterolemic diabetic patients. These outcomes suggest that while regular doses of *S. officinalis* have antioxidant properties and can enhance lipid profiles, higher doses or more concentrated extracts might be necessary to significantly affect glycemic indices, particularly in diabetic or prediabetic individuals. Additionally, for tea consumption or lower doses, extending the duration of the intervention may be beneficial.

Two systematic reviews and meta-analyses have explored the lipid-lowering and blood sugar-reducing capabilities of *S. officinalis*. Despite the limited number of studies included, these reviews have shown promising results for *S. officinalis* in enhancing serum lipid and glucose levels in clinical settings, positioning it as a viable plant-based option for managing metabolic conditions [16, 36].

Various animal studies have also assessed the impact of *S. officinalis* on metabolic disorders such as diabetes and hyperlipidemia. In a study, in mice on a high-fat diet, the effects of *S. officinalis* essential oil were compared with simvastatin [31]. *S. officinalis* essential oil alongside simvastatin, administered at 4 mg/kg for eight weeks, led to reductions in body weight gain, lipid levels, liver and kidney function disruptions, and reactive oxygen species production. Notably, this study suggested that the essential oil's lipid-lowering effect surpassed that of simvastatin. Another study, demonstrated that *S. officinalis* Aqueous Extract, given at 150 mg/kg, significantly normalized body weight, glucose, insulin, leptin,

Table 2 Comparison of lipid profile parameters between two groups

		S. officinalis	Placebo	Diff[a]	95% CI		*P*[†]	*P*[§]
		Mean ± SD	Mean ± SD		Lower	Lower		
TG (mg/d)	**Pre**	107.73 ± 30.14	112.36 ± 37.55	−4.63	−21.98	12.71	0.595	**0.000**
	Post	94.23 ± 30.24	111.48 ± 35.70	−17.25	−34.35	−0.14	**0.048**	
	Change	−13.50 ± 10.80	−0.88 ± 6.99	−12.61	−17.32	−7.91	**0.000**	
TC (mg/d)	**Pre**	170.90 ± 30.14	163.00 ± 27.76	7.90	−7.07	22.87	0.295	0.305
	Post	163.03 ± 29.58	162.28 ± 23.23	0.74	−13.00	14.49	0.914	
	Change	−7.86 ± 14.17	−0.713 ± 19.13	−7.15	−15.85	1.54	0.105	
HDL-C (mg/d)	**Pre**	47.36 ± 8.03	51.10 ± 9.25	−3.73	−8.21	0.74	0.101	**0.047**
	Post	48.33 ± 10.14	50.86 ± 8.97	−2.53	−7.48	2.41	0.310	
	Change	0.96 ± 3.65	−0.23 ± 1.25	1.20	−0.21	2.61	0.094	
LDL-C (mg/d)	**Pre**	101.53 ± 30.83	89.00 ± 29.25	12.53	−3.67	6.33	0.112	0.522
	Post	95.36 ± 30.93	89.46 ± 24.25	5.90	−3.58	5.74	0.414	
	Change	−6.16 ± 15.02	0.46 ± 19.38	−6.63	−1.44	0.94	0.144	
LDL/HDL	**Pre**	2.26 ± 1.02	1.82 ± 0.77	0.43	−0.03	0.90	0.067	0.583
	Post	2.11 ± 0. 99	1.82 ± 0.61	0.29	−0.13	0.71	0.178	
	Change	−0.15 ± 0.40	−0.006 ± 0.41	−0.14	−0.35	0.06	0.172	
TG/HDL-C	**Pre**	2.39 ± 0.90	2.29 ± 0.96	0.09	−0.38	0.57	0.693	**0.000**
	Post	2.09 ± 0.94	2.29 ± 0.93	−0.19	−0.68	0.29	0.425	
	Change	−0.29 ± 0.31	−0.007 ± 0.18	−0.29	−0.42	−0.15	**0.000**	
TC/HDL-C	**Pre**	3.75 ± 1.14	3.29 ± 0.83	0.45	−0.06	0.97	0.083	0.353
	Post	3.54 ± 1.10	3.27 ± 0.64	0.27	−0.19	0.73	0.254	
	Change	−0.21 ± 0.43	−0.02 ± 0.41	−0.18	−0.40	0.03	0.090	

HDL-C High Density Lipoprotein Cholesterol, *LDL-C* Low Density Lipoprotein Cholesterol, *LDL/HDL* Low Density Lipoprotein Cholesterol to High-Density Lipoprotein Cholesterol Ratio, *SD* Standard Deviation, *TC* Total Cholesterol, *TC/HDL-C* Total Cholesterol to High-Density Lipoprotein Cholesterol Ratio, *TG* Triglyceride, *TG/HDL-C* Triglyceride to High-Density Lipoprotein Cholesterol Ratio

[a] Mean Difference: Intervention minus control group

[†] Analysis was based on independent *t*-test

[§] Analysis was based on ANCOVA (the included covariates were: baseline value of dependent variable, age, BMI, and treatment type)

Table 3 Comparison of on markers of oxidative stress between two groups

		S. officinalis	Placebo	Diff[a]	95% CI		*P*[†]	*P*[§]
		Mean ± SD	Mean ± SD		Lower	Upper		
MDA (µM)	**Pre**	16.14 ± 7.19	15.27 ± 6.37	0.86	−2.64	4.38	0.623†	**0.000**
	Post	11.41 ± 4.82	14.86 ± 6.12	−3.44	−6.29	−0.59	**0.019**	
	Change	−4.72 ± 3.73	−0.41 ± 1.16	−4.31	−5.74	−2.88	**0.000**	
TAC (µM/L)	**Pre**	0.546 ± 0.062	0.525 ± 0.083	0.021	0.016	−0.059	0.124†	**0.024**
	Post	0.553 ± 0.069	0.517 ± 0.084	0.035	−0.004	0.075	0.080	
	Change	0.006 ± 0.012	−0.007 ± 0.029	0.014	0.002	0.026	**0.020**	

CI Confidence Interval, *MDA* Malondialdehyde, *SD* Standard Deviation, *TAC* Total Antioxidant Capacity

[a] Mean Difference: Intervention minus control group

[†] Analysis was based on independent *t*-test

[§] Analysis was based on ANCOVA (the included covariates were: baseline value of dependent variable, age, BMI, and treatment type)

adiponectin, cholesterol levels, and OS and inflammatory markers in plasma and liver tissue of rats with diet-induced obesity after eight weeks [32].

Research on the efficacy of *S. officinalis* in treating reproductive disorders is limited. The study by Ghowsi et al. [44] is particularly relevant to our focus, as it demonstrated that sage tea consumption could improve serum total antioxidant capacity and influence lipid profiles in a PCOS rat model. Their findings indicated that sage tea consumption improved serum total antioxidant

capacity and reduced HDL-C, glucose, total cholesterol, LDL-C, and the atherogenic index, although it did not affect MDA, insulin, total triglycerides, and VLDL-C levels. However, there are other studies like [37] and [51], while not directly examining lipid profile outcomes, offer insights into the potential reproductive health benefits of *S. officinalis*, such as enhanced ovarian function and fertility. These findings, though not directly aligned with our study's parameters, contribute to the broader understanding of *S. officinalis*'s therapeutic potential in reproductive health. Further research is needed to fully elucidate the effects of *S. officinalis* on reproductive disorders and its potential integration into treatment protocols.

Study limitations and recommendations for future studies

The first important point to consider is that the cultivation environment of *S. officinalis*, including climate, altitude, and shade conditions, can influence the plant's chemical composition and the potency of its active ingredients. This limitation means that the findings of the present study are specific to the Iranian native *S. officinalis* cultivated in Fars and Isfahan provinces, with their hot and dry climates and unique geographical features. Thus, examining the effects of other *S. officinalis* species from different regions around the world could provide additional insights. On the other hand, we acknowledge the significance of understanding the biochemical profile of the plant extract. Although we did not conduct chromatographic assessments in this study, several well-designed investigations have explored the chemical composition, phytochemical profile, and activity relating to anti-inflammatory, antioxidative, and cholinesterase effects in various Iranian native Salvia species, including *S. officinalis* [52, 53].

Another consideration is that, as highlighted in various studies, the outcomes of *S. officinalis* treatments can vary widely based on factors such as the duration of treatment, dosage, type of extract used (whether aqueous, hydroalcoholic, alcoholic, or essential oil), method of administration (tea, dry powder, capsule, or liquid), and the specific parts of the plant utilized. The findings of the present study are limited to the dosage, duration, and type of extract investigated. Therefore, future studies are recommended to assess the effects of other dosages, durations, and administration forms of *S. officinalis* to provide more comprehensive evidence regarding the efficacy and toxicity of this herb.

Additionally, according to our findings, the administration of *S. officinalis* at normal doses demonstrated acceptable antioxidant effects and improved lipid profiles in normolipidemic and euglycemic PCOS patients. However, in individuals with diabetes or pre-diabetic conditions, higher doses and extracts with greater concentrations may be necessary, especially in cases where other forms of extract or tea consumption are involved.

One limitation of our research was the inclusion of all PCOS phenotypes, which may exhibit varying levels of dyslipidemia and OS. It is crucial for future research to identify which PCOS phenotypes respond most favorably to *S. officinalis* treatment. The Rotterdam criteria classify PCOS into four phenotypes, each presenting unique symptoms and challenges:

- Phenotype A: Hyperandrogenism (HA) + Ovulatory Dysfunction (OvDys) + Polycystic Ovarian Morphology (PCOM)
- Phenotype B: HA + OvDys
- Phenotype C: HA + PCOM
- Phenotype D: OvDys + PCOM

Hyperandrogenism is primarily diagnosed by symptoms such as hirsutism (excessive hair growth) and acne, but it can also be confirmed through paraclinical investigations of circulating androgen levels (hyperandrogenemia). Ovulatory dysfunction is often detected based on symptoms like irregular or absent menstrual periods (oligoamenorrhea), and it can also be diagnosed through hormonal assessments. PCOM is defined by ultrasound findings showing multiple cysts on the ovaries [54].

The bioactive compounds in sage, such as rosmarinic acid and carnosic acid, may help reduce androgen levels, alleviating symptoms like excessive hair growth and acne. By improving hormonal balance, sage may help regulate menstrual cycles, addressing ovulatory dysfunction [37]. The anti-inflammatory activity and antioxidant properties of sage also may reduce PCOS-associated reproductive disorders including ovarian cyst formation and compromized oocyte quality [11, 55].

However, all of these proposed potential effects on PCOS-associated symtomes should be examined comprehensively in in-vitro and clinical settings. To identify which phenotype would benefit most from *S. officinalis*, it is crucial to record the underlying symptoms. Future studies should adopt a symptom-based approach and measure levels of reproductive hormones. This approach will help determine the specific benefits of *S. officinalis* for each phenotype and provide a more personalized treatment strategy.

Additionally, women with PCOS often experience psychological symptoms and brain activity alterations, which negatively impact their quality of life. These symptoms include mood disorders, anxiety, and cognitive impairments such as deficits in attention and memory [56]. So, it would be beneficial to explore the potential cognitive and emotional benefits of *S. officinalis*, particularly its

action on cholinergic function [57, 58]. *S. officinalis* is known for its action on cholinergic function, which could be beneficial for cognitive improvement and emotional regulation [59]. Future studies could also investigate the relationship between acetylcholinesterase (AChE) regulation and OS. This could provide insights into the long-term cognitive and emotional effects of prolonged lipid and glycemic regulation alterations. Plants rich in antioxidants and anti-inflammatory bioactives, such as sage, could help normalize these functions and improve overall well-being in PCOS patients.

One of the other limitations of our study is that our manuscript does not include an assessment of androgenes and gonadotropin levels, which are critical in understanding the hormonal dynamics in PCOS. Given the limitations of our current study, we recommend that future research should include a comprehensive assessment of androgen and gonadotropin levels to better understand the hormonal dynamics in PCOS. Specifically, measuring levels of androgens, estradiol (E2), progesterone, luteinizing hormone (LH), and follicle-stimulating hormone (FSH) could provide valuable insights into the metabolic and endocrine effects of *S. officinalis*. Incorporating these hormonal assessments will help elucidate the endocrine effects of sage and offer a more holistic understanding of its therapeutic potential in PCOS management. Additionally, this approach will provide more robust evidence regarding the impact of *S. officinalis* on reproductive function and female fertility.

However, several important considerations must be addressed in future studies. First, our study primarily focused on metabolic outcomes based on existing literature that highlights the metabolism-regulating features of sage. The dosage and duration used in our study were selected to align with these findings. Future studies should consider whether the proposed duration and dosage are sufficient to produce significant and measurable effects on gonadotropic hormones and androgen levels, as well as to alleviate symptoms such as oligomenorrhea and hirsutism.

Second, treatments for PCOS-associated reproductive problems or hyperandrogenism typically require longer durations to show noticeable effects. Future research should explore the effects of longer treatment durations and potentially higher doses. Preliminary pilot trials will be necessary to adjust dosages appropriately.

The third point is about safety considerations. Given the higher susceptibility of gametes (oocytes) and embryos to external and environmental exposures, including natural herbs, it is crucial to conduct more studies to determine the safety of *S. officinalis*'s dosage and duration. The current evidence on *S. officinalis*'s teratogenic potential is insufficient to support its use in infertility treatment programs. Therefore, further research is needed to ensure the safety and efficacy of sage in this context and also exploring the its long-term effects.

Moreover, it would be beneficial for subsequent studies to evaluate the efficacy of *S. officinalis* in conjunction with lifestyle modifications, such as diet and exercise, which are typically recommended as the initial approach to prevent metabolic disorders in women with PCOS. Additionally, future research could explore combining sage with medical PCOS treatment methods, including antiandrogenic agents, oral contraceptives, and ovulation-inducing agents such as clomiphene citrate or gonadotropins.

Future studies should also focous on *S. officinalis*'s specific mechanisms of action in reproductive system. There are various invitro, invivo, and secondary studies including network pharmacology that provided valuable body of evidence exploring the molecular signaling pathways affected by *S. officinalis*. But all these investigation are based on diabetes and metabolic context [60–62]. The evidence regarding S. officinalis's poteintial machenism of actionin reproductive conditions is limitted.

Focusing just on the 15–40-year-old Iranian population is another factor that might affect the generalizability of our findings. Cultural, dietary, and lifestyle factors specific to this group may influence the outcomes. These factors may differ significantly from those in other ethnic or cultural groups, potentially affecting the generalizability of the results. Also, the age range of 15–40 years was chosen to include women of reproductive age who are most commonly affected by PCOS. However, PCOS can present differently in younger adolescents and older women, and the findings may not be directly applicable to these age groups. To enhance the generalizability of future studies, we recommend future studies to include participants from diverse ethnic, cultural, and geographic backgrounds to better understand the effects of *S. officinalis* across different populations. Also, including other age groups, including adolescents and older women, can help determine the efficacy and safety of *S. officinalis* in different age groups. By addressing these limitations and incorporating a more diverse study population, future research can provide a more comprehensive understanding of the potential benefits of *S. officinalis* for PCOS patients.

Finally we recommned future studies to implement more options for monitoring participant compliance with the treatment regimen. We used weekly phone calls and a paper-based table to monitor adherence, common methods in clinical trials that effectively ensure participant compliance. Given our country's facilities and participants' capabilities, these were the best options. While not all participants had access to online tools or

smartphones, they could utilize a printed table for compliance monitoring, regardless of literacy skills. This can include electronic monitoring devices such as mobile apps that remind participants to take their supplements and allow them to record their adherence in real time. Combining paper-based tables with digital diaries or online surveys can also reduce the risk of data loss and improve the ease of reporting for participants.

Conclusion

In conclusion, this study contributes to the growing body of evidence that *S. officinalis* positively affects lipid profiles and OS markers, presenting a promising natural intervention for the prevention and management of metabolic disorders associated with PCOS. However, future research should take a symptom-based approach and include a thorough assessment of androgen and gonadotropin levels to clarify the effects of *S. officinalis* on reproductive issues linked to PCOS. Additionally, given the methodological limitations of the current study, further research with larger sample sizes that includes participants from diverse ethnic, cultural, and geographic backgrounds is necessary. Investigating different dosages, durations, and forms of *S. officinalis* extract will also be important to fully understand its benefits and applications in clinical practice.

Abbreviations

PCOS	Polycystic ovary syndrome
OS	Oxidative stress
S. officinalis	Salvia officinalis L.
PPARγ	Peroxisome proliferator-activated receptor γ
TC	Total cholesterol
LDL-C	Low-density lipoprotein cholesterol
HDL-C	High-density lipoprotein cholesterol
TG	Triglycerides
LDL/HDL	LDL to HDL ratio
TC/HDL-C	TC to HDL-C ratio
TG/HDL-C	TG to HHDL-C ratio
MDA	Malondialdehyde
TAC	Total antioxidant capacity

Supplementary Information

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Supplementary Material 1.

Authors' contributions

All authors contributed to the study conception and design and commented on previous versions of the manuscript. All authors read and approved the final manuscript. A detailed contribution statement is provided below: AM-H: Design of study, data collection, manuscript original draft preparation, statistical analyses, and graphical abstract designing; FM: Design of study, preparation of extracts, interpretation of results, and critical revision of the manuscript for important intellectual content; FA: Data collection, interpretation of results, and critical revision of the manuscript for important intellectual content; LA: Conception and design of study, supervision, interpretation of data, manuscript original draft preparation.

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Data availability

The data collection forms and data used for analyses are not publicly available, however, they will be provided by the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

The study was designed and performed according to the Declaration of Helsinki and all participants signed an informed consent. Study protocol was approved by the Ethics Committee of Iran University of Medical Sciences (code of ethics is IR.IUMS.REC.1394.9211373221).

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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