



# Comparing the effects of nettle extract with combined oral contraceptives on improving clinical and paraclinical symptoms of polycystic Ovary Syndrome: A triple-blind randomized controlled clinical trial

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## Abstract

**Background:** Polycystic Ovary Syndrome (PCOS) is one of the most significant reproductive and endocrine disorders in women. This study aims to assess the impact of nettle extract on both clinical and paraclinical symptoms in women with PCOS.

**Methods:** This Triple-Blind Randomized Controlled Clinical Trial involved 60 women (n = 30 per group) aged 18 to 45, all diagnosed with PCOS based on definitive diagnostic criteria in Tabriz, Iran. Participants were randomly assigned in a 1:1 ratio using block sizes of 4 and 6 into two groups: an intervention group (Receiving 500 mg of oral nettle extract containing flavonoids, tannins, and sterols daily for three months) and a control group (Receiving combined oral contraceptives [COCs] for three months). Independent t-test and ANCOVA test were used in SPSS version 24 for data analysis. A p-value of <0.05 was considered statistically significant.

**Results:** The study showed that after the intervention, there were no statistically significant differences between the nettle extract group and the control group regarding mean levels of dehydroepiandrosterone sulfate (P=0.197), total testosterone (P=0.24), follicle-stimulating hormone (FSH) (P=0.549), luteinizing hormone (LH) (P=0.398), hirsutism score (P=0.149), or duration of menstrual bleeding (P=0.982), based on ANCOVA adjusted for baseline values, education level, and number of pregnancies. However, the two groups exhibited statistically significant differences in fasting blood glucose levels (P=0.020), intervals between menstrual bleeding (days) (P=0.031), and menstrual bleeding intensity (P = 0.008).

**Conclusion:** The findings indicate that nettle extract is as effective as low-dose oral contraceptive pills in reducing levels of dehydroepiandrosterone, total testosterone, follicle-stimulating hormone (FSH), and luteinizing hormone (LH), as well as in decreasing hirsutism scores and the duration of menstrual bleeding. Midwives can use nettle extract, which is a cheap, easy, and non-invasive method to improve PCO symptoms.

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## Highlights

### What is current knowledge?

Nettle (*Urtica dioica*) possesses several medicinal properties, including antioxidant, anti-inflammatory, anti-ulcer, anticancer, and antibacterial and antifungal effects. Additionally, it may contribute to the improvement of clinical and paraclinical symptoms associated with Polycystic Ovary Syndrome (PCOS).

### What is new here?

The findings indicate that nettle extract is effective in reducing levels of dehydroepiandrosterone, total testosterone, follicle-stimulating hormone (FSH), and luteinizing hormone (LH). Moreover, it significantly decreases hirsutism scores and the duration of menstrual bleeding.

## Introduction

Polycystic Ovary Syndrome (PCOS) is the most common endocrine reproductive disorder worldwide. The prevalence of PCOS according to the diagnostic criteria of the NIH, Rotterdam and AE-PCOS Society were 13.6, 19.4, and 17.8, respectively (1). PCOS is characterized by chronic oligo- or anovulation, polycystic ovarian morphology, clinical or biochemical signs of hyperandrogenism, and is often associated with metabolic disturbances-primarily insulin resistance and compensatory hyperinsulinemia (2,3).

PCOS is a significant contributor to female infertility and other various metabolic disorders. It has been reported as the cause of infertility in 70% of affected women. PCOS was diagnosed in three out of every ten infertile women (4). Women with PCOS face a higher risk of miscarriage (5,6) and pregnancy complications, including gestational diabetes, hypertension, and preterm labor (6). Additionally, the risk of developing endometrial hyperplasia and endometrial cancer is up to four times higher compared to women without PCOS (7,8). Cardiovascular disorders, such as dyslipidemia, hypertension, and obstructive sleep apnea, are also more prevalent in this syndrome (9,10). Due to distress caused by hyperandrogenic symptoms (Such as acne, hirsutism, alopecia, and male-pattern baldness), weight gain, and infertility, women with PCOS often experience mood disorders (11,12).

The Rotterdam diagnostic criteria are commonly used worldwide to diagnose PCOS (13). When menstrual cycles are irregular or absent, a diagnosis of PCOS should be considered, as approximately 85-90% of women with oligomenorrhea and 30-40% of women with amenorrhea are affected by PCOS (14).

Lifestyle interventions, including a combination of a healthy diet and increased physical activity (15,16), as well as the use of combined oral contraceptive pills (COCs), are recommended as the first-line medical treatment for managing hyperandrogenism and regulating menstrual cycles in women with PCOS (17,18). Medications such as metformin and anti-androgens like flutamide and spironolactone are

also effective in managing the condition (19,20).

Women with PCOS may have contraindications to the use of oral contraceptive pills (OCPs) (21). Although ovulation induction with clomiphene has been successful, pregnancy rates remain inexplicably low (22). Up to 30% of women with PCOS—particularly those who are overweight—do not respond to clomiphene treatment (22–24). Metformin is effective in improving insulin sensitivity and hyperandrogenism; however, its use is often associated with a high incidence of side effects, including nausea, vomiting, and gastrointestinal disturbances (25).

The World Health Organization recommends using herbal medicines and encourages researchers to incorporate medicinal plants into traditional medicine practices for their preventive, therapeutic, and rehabilitative roles (26). Herbal treatments may serve as highly effective therapeutic options for PCOS due to their fewer side effects compared to chemical medications (27). Nettle (*Urtica dioica*) is a perennial herbaceous plant belonging to the Urticaceae family. It grows in temperate and tropical wastelands worldwide and is distributed across Iran's northern, northwestern, and central regions. The plant includes about 60 genera and 700 species (28) and is classified as a key medicinal plant in the European Pharmacopoeia. Nettle possesses several medicinal properties, including antioxidant (29), anti-inflammatory, anti-ulcer (30), anticancer (31), and antibacterial and antifungal effects (32).

Flavonoids, tannins, scopoletin, sterols, fatty acids, polysaccharides, isolectins, and sterols are phytochemicals reported from this plant. Due to its ease of collection, wide availability, and significant biological activities, nettle has been transformed into medicine and food in many countries, particularly in the Mediterranean region (28). Nettle extract is effective in controlling morphological and histological changes in polycystic ovaries, as well as complications related to metabolic syndrome and alterations in sex hormones in a mouse model of PCOS (33).

In studies conducted on rats, mice, dogs, chickens, and cell culture models, the effects of nettle extract have been shown to control inflammatory cytokines, clinical symptoms, immune responses, blood glucose levels, glucose transporter gene expression, and lipid peroxidation in various organs (34,35). Nettle's ability to regulate lipid profiles and enhance insulin sensitivity is believed to alleviate some common symptoms of metabolic syndrome and type 2 diabetes in PCOS, an effect attributed to its flavonoid compounds (36).

Given the side effects associated with chemical medications in the treatment of PCOS, the use of herbal remedies with therapeutic effects and fewer adverse reactions is expanding (37). Based on a search of electronic databases, aside from one animal study, no human research has been found regarding the effects of nettle extract on the clinical and paraclinical symptoms of PCOS in women. Considering the high prevalence of PCOS among women of reproductive age and its negative impact on their quality of life, this study was conducted to evaluate the effects of nettle extract compared to combined oral contraceptives (COCs) on the clinical and paraclinical manifestations of PCOS in affected women.

## Methods

### Study design and sampling

This study was a triple-blind randomized controlled trial, involving participants, researchers, and data analysts who were all unaware of the type of intervention. It employed a parallel design and was conducted between December 2022 and April 2025, following the acquisition of the necessary approvals from the Research Ethics Committee. The study included 60 women ( $n = 30$  per group) aged 18 to 45 years who visited the clinics of Tabriz University of Medical Sciences and the Faculty of Traditional Medicine in Iran. Participants were diagnosed with PCOS according to the Rotterdam criteria, which require the presence of two out of three criteria: clinical or biochemical hyperandrogenism, menstrual cycle disturbances, or polycystic ovarian ultrasound findings. Eligible participants were selected by the researcher based on the inclusion criteria. The objectives and procedures of the study were explained, and written informed consent was obtained from those willing to participate. Additionally, participants completed demographic and menstrual cycle questionnaires, which were recorded in a checklist.

The primary outcomes of this study included levels of hirsutism. In contrast, the secondary outcomes encompassed paraclinical criteria such

as follicle-stimulating hormone (FSH), luteinizing hormone (LH), fasting blood sugar (FBS), and testosterone levels, as well as clinical criteria including menstrual cycle intervals, duration, and bleeding intensity.

The inclusion criteria for this study were as follows: a confirmed diagnosis of PCOS according to the Rotterdam criteria; women aged 18 to 45 years; the ability to read and write; a body mass index between 18.5 and 30; no use of hormonal contraceptive medications; any other hormonal drugs currently or vitamin and minerals supplements within the past three months; and no desire for pregnancy. The exclusion criteria included both relative and absolute contraindications for low-dose (LD) pills, such as having a blood pressure above 140/90 mmHg, pregnancy or breastfeeding, alcohol and tobacco use, suspicion of breast cancer, coronary heart disease, or endometrial carcinoma. Additionally, women undergoing infertility treatment at the time of the study, those with a history of previous surgery on one or both ovaries, allergies to nettle, pregnancy and those with disorders that cause hyperandrogenism (Such as Cushing's syndrome, adrenal hyperplasia, androgen-producing tumors) were also excluded.

Participants were randomly allocated into two groups (Intervention and control) using block randomization with block sizes of 4 to 6 and a 1:1 allocation ratio. The allocation sequence was determined by a person not involved in the study, using the RAS (Random Allocation Software) version 1.0.0. Participants in both groups received education on a healthy lifestyle (Nutrition and physical activity) from the researcher, and they were instructed and emphasized not to attempt pregnancy during the treatment period and to use a reliable non-hormonal contraceptive method.

To conceal the drug allocation, the treatments or controls were placed in opaque envelopes, sequentially numbered from 1 to 60. This preparation was carried out according to the allocation sequence by an individual not involved in the study. The intervention lasted for 3 months. Participants in the intervention group received 500 mg nettle extract capsules (Containing flavonoids, tannins, and sterols), taking one capsule daily (30 capsules in total), which were prepared and packaged by Sina Novandish Company in Tabriz, Iran. Subsequently, the Pharmaceutical Research Department of the Faculty of Pharmacy analyzed and confirmed the contents. Participants in the control group received LD capsules (Containing 30 micrograms of ethinylestradiol and 150 micrograms of levonorgestrel), which included 21 active capsules and nine placebo capsules for a 30-day cycle. These were packaged and numbered identically to the nettle capsules (Ensuring the participant would begin with the LD capsules and finish with the placebo). These capsules were also prepared by Sina Novandish Company. To ensure blinding between the study and control groups, 30 nettle or LD capsules were placed in similar containers. The LD tablets were housed inside the capsules, with 21 of the capsules being green and nine oranges. To minimize gastrointestinal side effects, the medication was taken at night after dinner. Only a one-month supply was provided to promote adherence, with participants instructed to obtain the remaining medication in subsequent visits. The envelopes, along with a daily medication checklist and a side effects log, were supplied.

Blood samples were drawn from the brachial vein before the intervention, after 8-hour fasting period, using a 5 mL syringe. The samples were placed in test tubes and immediately sent to the laboratory. Following centrifugation at 3000 rpm, the serum samples were transferred to 1.5 mL microtubes and stored at  $-70^{\circ}\text{C}$  until analysis. In this study, serum levels of blood tests were measured using the enzyme-linked immunosorbent assay (ELISA) method at the provincial laboratory. To assess the reliability of the instrument, a separate sample of five women was prepared and provided to the experimenter under two different names, without disclosing the study group designation. The results were analyzed using the Pearson correlation coefficient, which yielded a correlation coefficient of  $r = 0.89$ , indicating a strong level of correlation.

A daily medication checklist was provided to participants to assess drug adherence, allowing them to mark off each dose taken. They were also asked to bring their medication packets to each visit to check the number of doses consumed and remaining. Additionally, a side effect report form was given to them to record any adverse effects after taking the medication. The potential side effects were fully explained to the participants, and they were advised to notify the researcher if they

experienced any. Every night, a reminder to take the medication was sent via SMS, and a weekly phone call was made to encourage participants to stay in the study. At the end of week 12, the hirsutism scale and menstrual disturbance questionnaires were completed again, and blood samples were taken.

### Sample size

The sample size was calculated using G-Power software (Version 3.1.9.4) based on the study by Attarzadeh (38) related to dehydroepiandrosterone (DHEA), with  $M1 = 2204$  and assuming a 10% reduction due to the intervention ( $M2 = 1763$ ), with  $SD1 = SD2 = 640$ ,  $\alpha = 0.05$ , and 80% power, the sample size was calculated to be 27 participants. Considering a potential 10% dropout rate, the final sample size was adjusted to 30 participants per group. Given the higher sample size based on the DHEA variable, the final sample size for this study was determined to be 30 participants in each group.

### Data collection tools

**Sociodemographic questionnaire:** This questionnaire included questions about age, marital status, occupation, monthly income, education, living conditions, number of pregnancies, number of deliveries, number of living children, number of miscarriages, and history of infertility.

**Menstrual cycle profile questionnaire:** This questionnaire addressed menstrual cycle status, including questions about the intervals, duration, and amount of menstrual bleeding over the past three months. It was completed at the beginning of the study and again three months after the intervention. The Higam Chart (Higham, 1990) was used to assess bleeding volume. This visual tool evaluates the amount of menstrual blood loss, assigning a score of 1 for a sanitary pad with slight blood staining, 5 for a half-soaked pad, and 20 for a completely soaked pad. Clots received scores from 1 to 5 based on their size. The chart records menstruation days in the horizontal row and stained pads according to their saturation level in the vertical row. Three levels of bleeding severity (Mild, moderate, and severe) were marked for each corresponding day. At the end of menstruation, each symbol was multiplied by its score to calculate the total score. A score below 50 indicated mild bleeding, between 51 and 100 indicated moderate

bleeding, and above 100 indicated heavy bleeding during menstruation. This standard questionnaire does not require validity determination (39).

**Hirsutism questionnaire:** The Ferriman-Gallwey score was used to evaluate hirsutism before and three months after the intervention. This scale assesses hair growth in nine body (Chin, sternum, thigh, scapula, arm, pubis, upper lip, abdomen, upper sacrum) areas and is scored on a Likert scale from 0 to 4, where 0 means no hair and 4 means excessive hair growth. The maximum score for an individual was 36, and the minimum score was 0 (40). This standard questionnaire does not require validity determination and was tested for reliability using inter-rater reliability (Kappa=0.89).

**Adverse event checklist:** This checklist records any adverse events that occurred during the study and their severity.

**Daily medication consumption checklist:** The daily medication and side effects form was filled out each day to ensure that pills were taken and to track any side effects, completed within 30 minutes after taking the medication.

### Data analysis

The Kolmogorov-Smirnov test was used to check the normality of the data. The Independent T-test and Chi-square test were used to compare demographic characteristics. The Independent T-test was applied to compare the mean hirsutism scores, laboratory values, menstrual cycle frequency, and duration before the intervention. After the intervention, ANCOVA (Analysis of Covariance) was used with baseline values as a covariate (Education and number of pregnancies). The Chi-square test was used to compare menstrual bleeding between two groups. A p-value of  $<0.05$  was considered statistically significant. The data were analyzed using SPSS software version 26. The analysis approach was based on Intention to Treat (ITT).

A total of 86 participants were evaluated, with 16 excluded based on the established criteria. Ten individuals met the inclusion criteria but withdrew from the study due to lack of consent. Therefore, 60 women aged 18 to 45 years with PCOS who met all the inclusion criteria were enrolled after obtaining informed consent. They were randomly assigned to either the intervention or control group. No participants were lost to follow-up during the third month, and after 12 weeks, 60 participants were re-evaluated (Figure 1).

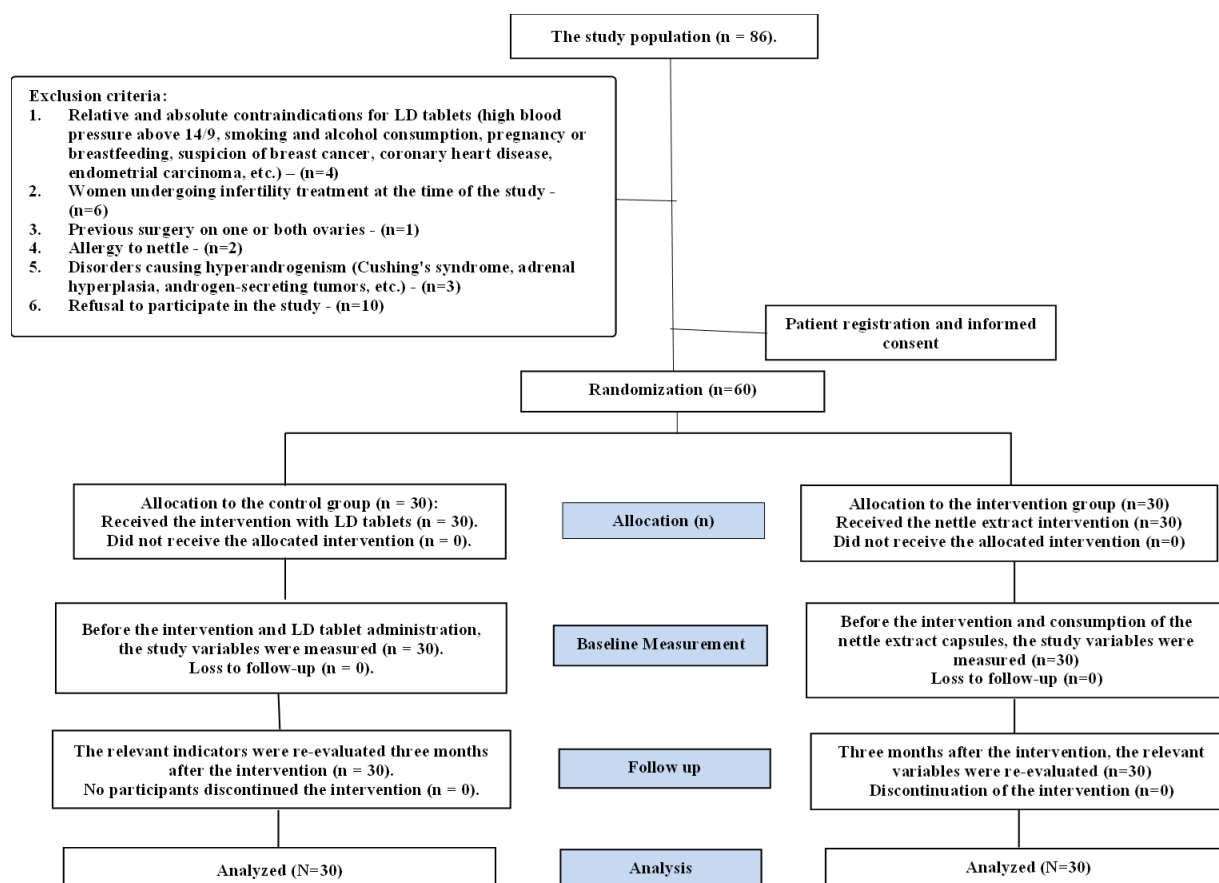


Figure 1. Study flowchart

## Results

The demographic and obstetric characteristics are presented in Table 1. According to the statistical results, there was no significant difference between the study and control groups, except for the education level and the number of pregnancies (Table 1).

Based on the ANCOVA test, after controlling for baseline values and the variables of education and number of pregnancies, there was no significant statistical difference between the two groups regarding serum levels of dehydroepiandrosterone (DHEA) (Mean difference: -18.68 µg/dL, 95% confidence interval: -47.31 to 9.97,  $P = 0.197$ ), total serum testosterone (Mean difference: 1.88 ng/dL, 95% confidence interval: -1.34 to 1.88,  $P = 0.24$ ), follicle-stimulating hormone (FSH) (Mean difference: 0.268 IU/L, 95% confidence interval: -1.60 to 1.23,  $P = 0.549$ ), and luteinizing hormone (LH) (Mean difference: -2.91 IU/L, 95% confidence interval: -3.92 to 9.73,  $P = 0.398$ ). However, the two

groups showed a significant statistical difference in fasting blood glucose levels (Mean difference: -3.13 mg/dL, 95% confidence interval: -5.75 to -0.52,  $P = 0.020$ ) (Table 2).

After the intervention, the mean (Standard deviation) cycle length in the nettle extract group was 38.43 (11.66) days, and in the control group, it was 31.00 (5.79) days (Mean difference: 5.20, 95% confidence interval: 0.49 to 9.91,  $P = 0.031$ ). Based on the ANCOVA test, while controlling for baseline values, education, and the number of pregnancies, a significant statistical difference between the two groups was noted for this measure. However, after the intervention, the duration of menstrual bleeding in the nettle extract group remained 6.43 (1.8) days, and in the control group, it remained 6.30 (2.2) days. The ANCOVA test, with baseline values, education, and the number of pregnancies controlled, indicated no significant statistical difference between the two groups for this measure (Mean difference: 0.08, 95% confidence interval: -0.70 to 0.72,  $P = 0.982$ ) (Table 3).

**Table 1.** Comparison of socio-demographic characteristics between study groups

| Variable                  | Nettle Extract (n=30) | Control (n=30) | P-Value  |
|---------------------------|-----------------------|----------------|----------|
| Mean (Standard Deviation) |                       |                |          |
| Age (Years)               | 24.90 (5.35)          | 27.33 (5.76)   | 0.095*   |
| Body Mass Index (kg/m²)   | 24.50 (2.75)          | 25.03 (2.79)   | 0.459*   |
| Number (Percentage)       |                       |                |          |
| Marital status            |                       |                |          |
| Married                   | 14 (46.7%)            | 12 (40.0%)     | 0.180**  |
| Single                    | 16 (53.3%)            | 18 (60.0%)     |          |
| Total                     | 30 (100%)             | 30 (100%)      |          |
| Employment status         |                       |                |          |
| Student                   | 12 (40.0%)            | 12 (40.0%)     | 0.083**  |
| Homemaker                 | 13 (43.3%)            | 11 (36.7%)     |          |
| Employed outside the home | 5 (16.7%)             | 7 (23.3%)      |          |
| Total                     | 30 (100%)             | 30 (100%)      |          |
| Income sufficiency        |                       |                |          |
| Fully sufficient          | 6 (20.0%)             | 3 (10.0%)      | 0.052*** |
| Somewhat Sufficient       | 24 (80.0%)            | 24 (80.0%)     |          |
| Not Sufficient            | 0 (0.0%)              | 3 (10.0%)      |          |
| Total                     | 30 (100%)             | 30 (100%)      |          |
| Education level           |                       |                |          |
| Below High School         | 4 (13.3%)             | 0 (0.0%)       | 0.004*** |
| High School               | 16 (53.3%)            | 11 (36.7%)     |          |
| University                | 10 (33.3%)            | 19 (63.3%)     |          |
| Total                     | 30 (100%)             | 30 (100%)      |          |
| Number of pregnancies     |                       |                |          |
| 0                         | 22 (73.3%)            | 24 (80.0%)     | 0.002**  |
| 1                         | 5 (16.7%)             | 0 (0.0%)       |          |
| 2                         | 3 (10.0%)             | 6 (20.0%)      |          |
| Total                     | 30 (100%)             | 30 (100%)      |          |
| Number of miscarriages    |                       |                |          |
| 0                         | 27 (90.0%)            | 27 (90.0%)     | 0.665**  |
| 1                         | 3 (10.0%)             | 3 (10.0%)      |          |
| Total                     | 30 (100%)             | 30 (100%)      |          |
| History of infertility    |                       |                |          |
| 1                         | 4 (13.3%)             | 0 (0.0%)       | 0.056**  |
| 2                         | 26 (86.7%)            | 30 (100%)      |          |
| Total                     | 30 (100%)             | 30 (100%)      |          |

\*Independent Samples T-test

\*Chi-square test

\*\*Chi-square test for trend

After the intervention, the mean (Standard deviation) hirsutism score in participants from the nettle extract group was 6.7 (4.48), while in the control group, it was 6.83 (4.64). Based on the ANCOVA test, which controlled for baseline values and the variables of education and number of pregnancies, there was no statistically significant difference between the groups (Mean difference: -0.49, 95% confidence interval: -1.81 to 1.64,  $P = 0.149$ ) (Table 3).

The majority of participants in both groups showed moderate bleeding before the intervention, with 21 participants (70.0%) in the nettle extract group and 24 participants (80.0%) in the control group. According to the chi-square test, there was no statistically significant difference between the groups ( $P = 0.296$ ). After the intervention, most participants continued to experience moderate bleeding-26 participants

(86.7%) in the control group and 27 participants (90.0%) in the nettle extract group-while severe bleeding was noted in 3 cases within the nettle extract group. In contrast, no severe bleeding occurred in the control group. The chi-square test indicated a statistically significant difference between the groups ( $P = 0.008$ ) (Table 4).

Half of the participants in the nettle extract group (16 participants, 52.4%) and the control group (16 participants, 52.4%) reported relative satisfaction with the medication. According to the Mann-Whitney test, this difference between the two groups was not statistically significant ( $P = 0.360$ ).

According to the patients' statements, no side effects were reported in either the study or control groups, and all participants had taken the LD and nettle capsules according to the routine.

**Table 2.** Comparison of the mean serum levels of DHEA, total testosterone, fasting blood sugar, follicle-stimulating hormone (FSH), and luteinizing hormone (LH) between study groups

| Variables                                | Nettle Extract (n = 30)<br>Mean (SD) | Control (n = 30)<br>Mean (SD) | Mean Difference<br>(95% Confidence Interval) | P-Value |
|------------------------------------------|--------------------------------------|-------------------------------|----------------------------------------------|---------|
| <b>Dehydroepiandrosterone (µg)</b>       |                                      |                               |                                              |         |
| Before intervention                      | 217.61 (98.38)                       | 290.53 (159.09)               | -72.92 (-141.28 to -4.56)                    | 0.037*  |
| After intervention                       | 173.56 (87.37)                       | 230.91 (88.31)                | -18.68 (-47.31 to 9.97)                      | 0.197** |
| <b>P-Value</b>                           | < 0.001***                           | < 0.001***                    | -                                            | -       |
| <b>Total testosterone (dL)</b>           |                                      |                               |                                              |         |
| Before intervention                      | 3.89 (10.77)                         | 10.14 (15.86)                 | -6.24 (-13.24 to 0.76)                       | 0.08*   |
| After intervention                       | 3.58 (9.84)                          | 4.74 (7.91)                   | 1.88 (-1.34 to 5.10)                         | 0.24**  |
| <b>P-Value</b>                           | 0.049***                             | < 0.001***                    | -                                            | -       |
| <b>Fasting Blood Sugar (mg)</b>          |                                      |                               |                                              |         |
| Before intervention                      | 86.93 (10.53)                        | 87.46 (10.29)                 | -0.53 (-5.92 to 4.85)                        | 0.84*   |
| After intervention                       | 86.80 (9.57)                         | 90.30 (7.77)                  | -3.13 (-5.75 to -0.52)                       | 0.020** |
| <b>P-Value</b>                           | 0.045***                             | 0.041***                      | -                                            | -       |
| <b>Follicle-Stimulating Hormone (mg)</b> |                                      |                               |                                              |         |
| Before intervention                      | 4.69 (2.29)                          | 5.60 (2.62)                   | -0.92 (-2.19 to 0.36)                        | 0.15*   |
| After intervention                       | 4.03 (1.50)                          | 3.87 (1.88)                   | 0.268 (-0.623 to 1.16)                       | 0.549** |
| <b>P-Value</b>                           | 0.041***                             | 0.039***                      | -                                            | -       |
| <b>Luteinizing Hormone (mIU/mL)</b>      |                                      |                               |                                              |         |
| Before intervention                      | 11.34 (17.64)                        | 10.67 (7.31)                  | 1.93 (-1.10 to 4.96)                         | 0.201*  |
| After intervention                       | 8.74 (3.91)                          | 9.56 (6.71)                   | -2.91 (-9.73 to 3.92)                        | 0.398** |
| <b>P-Value</b>                           | < 0.001***                           | 0.049***                      | -                                            | -       |

\* Independent sample t-test

\*\*ANCOVA test controlling for baseline values and the variables of education and number of pregnancies

\*\*\* Paired sample t-test

**Table 3.** Comparison of menstrual cycle intervals, duration of bleeding, and hirsutism score between study groups

| Variables                               | Nettle Extract<br>(n = 30)<br>Mean (SD) | Control<br>(n = 30)<br>Mean (SD) | Mean Difference<br>(95% CI) | P-Value |
|-----------------------------------------|-----------------------------------------|----------------------------------|-----------------------------|---------|
| <b>Interval between bleeding (Days)</b> |                                         |                                  |                             |         |
| Before Intervention                     | 49.23 (20.1)                            | 46.67 (20.9)                     | 2.57 (-8.05 to 13.19)       | 0.631*  |
| After Intervention                      | 38.43 (11.66)                           | 31.00 (5.79)                     | 5.20 (0.49 to 9.91)         | 0.031** |
| <b>Duration of bleeding (Days)</b>      |                                         |                                  |                             |         |
| Before Intervention                     | 6.43 (1.8)                              | 6.30 (2.2)                       | 0.133 (-0.917 to 1.184)     | 0.821*  |
| After Intervention                      | 5.57 (1.70)                             | 5.57 (0.94)                      | 0.008 (-0.704 to 0.720)     | 0.982** |
| <b>Hirsutism score</b>                  |                                         |                                  |                             |         |
| Before Intervention                     | 9.73 (5.22)                             | 10.53 (5.96)                     | -0.80 (-3.70 to 2.09)       | 0.580*  |
| After Intervention                      | 6.70 (4.48)                             | 6.83 (4.64)                      | 0.491 (-0.181 to 1.164)     | 0.149** |

\* Independent sample t-test

\*\*ANCOVA test controlling for baseline values and the variables of education and number of pregnancies

**Table 4.** Comparison of bleeding intensity based on the Higham chart between study groups

| Variables               |          | Nettle Extract group<br>(n = 30) | Control group<br>(n = 30) | P-Value |
|-------------------------|----------|----------------------------------|---------------------------|---------|
| Bleeding intensity      |          |                                  |                           |         |
| Before the intervention | Mild     | 3 (10.0%)                        | 0 (0.0%)                  | 0.296*  |
|                         | Moderate | 21 (70.0%)                       | 24 (80.0%)                |         |
|                         | Severe   | 6 (20.0%)                        | 6 (20.0%)                 |         |
| After the intervention  | Mild     | 0 (0.0%)                         | 4 (13.3%)                 | 0.008*  |
|                         | Moderate | 27 (90.0%)                       | 26 (86.7%)                |         |
|                         | Severe   | 3 (10.0%)                        | 0 (0.0%)                  |         |

\*Chi-square test

## Discussion

This study aimed to compare the effects of nettle root extract with COCs on improving the clinical and paraclinical symptoms of PCOS. A randomized, controlled, triple-blind trial was conducted.

The results showed that after the intervention, there was no significant statistical difference between the serum levels of DHEA and total testosterone in the nettle extract group compared to the control group. The nettle extract and the COCs were equally effective in reducing these hormones.

In alignment with the goal of this study, a clinical trial conducted by Najafipour et al. (2014) aimed to evaluate the therapeutic effects of nettle in women with hyperandrogenism. In that study, total and free testosterone and DHEA serum levels were measured before and after the intervention. Patients were treated for 4 months with either standard treatment (Control group) or dried nettle root extract (Intervention group). The results showed a significant reduction in total and free testosterone levels in the nettle group post-treatment (41).

Regarding the aim of comparing the mean serum levels of gonadotropins (FSH and LH) in the intervention and control groups, the results indicated that after the intervention, there was no significant statistical difference in the mean serum levels of FSH and LH between the nettle extract group and the control group. Both nettle extract and COCs were equally effective in reducing these hormones.

Although no human studies were found directly related to this specific objective, a survey by Esfedehe and colleagues (2019) investigated the effect of nettle extract as a metformin supplement on ovarian tissue in a diabetic rat model. At the end of the treatment, the effects of metformin and nettle root extract on ovarian tissue and biochemical factors, such as blood glucose levels and sex hormones, were compared. After 4 weeks of treatment with metformin and nettle root extract, hyperglycemia and body weight reduction showed improvement. The simultaneous administration of metformin and nettle root extract resulted in a significant increase in primary and secondary follicles, as well as an increase in corpus luteum size, a reduction in atretic follicles, and a significant rise in the levels of FSH, LH, and testosterone, compared to metformin alone. This study concluded that nettle root, with its antioxidant properties and other bioactive components, can complement metformin, improving blood sugar levels and ovarian dysfunctions. Studies conducted in diabetic rats support the hypothesis that antioxidant compounds can ameliorate this pathogenesis, potentially due to their direct effects on insulin secretion, prevention of beta-cell death, or regulation of beta-cell proliferation (42).

The results showed that after the intervention, the mean (Standard deviation) fasting blood glucose levels in the participants of the nettle extract group had a statistically significant difference compared to the control group, indicating that the use of nettle extract affected fasting blood glucose levels. In a double-blind clinical trial conducted by Kianbakht et al. (2013), the effect of nettle leaf extract on controlling blood glucose in patients with advanced type 2 diabetes was investigated. The intervention group consisted of 46 patients who took 500 mg of nettle capsules orally every 8 hours for 3 months, while the control group received a placebo capsule under the same conditions. No side effects, including hypoglycemia, were reported. At the end of the study, nettle extract significantly reduced fasting glucose, postprandial glucose (2 hours after meals), and HbA1c levels. These results

demonstrate the positive effects of nettle extract on blood glucose control in patients with type 2 diabetes (43).

Three potential mechanisms for the effects of nettle in lowering blood glucose include: 1) the impact of nettle on muscle cells by increasing the formation of permeable pores, which enhances glucose uptake in muscles, ultimately leading to a reduction in blood glucose levels in type 2 diabetes. 2) Stimulating the release of insulin from beta cells. 3) The influence on carbohydrate hydrolysis inhibitors. Compounds (flavonoids, peptides, and amines) found in the nettle plant leaves are known to have anti-diabetic effects (44). However, a study by Esfedehe et al. (2019) aimed at determining the impact of nettle extract as a supplement to metformin on ovarian tissue in a diabetic rat model demonstrated that the antioxidant properties of nettle are attributed to its flavonoid compounds (42).

Regarding the goal of normalizing menstrual cycles in both groups, the results showed that COCs were more effective than nettle extract in regulating the intervals between menstrual cycles. Additionally, the study results indicated that nettle extract was as effective as COCs in reducing the duration of menstrual bleeding.

A study conducted by Najafipour and colleagues (2014) aimed to determine the effect of nettle on women with hyperandrogenism. It showed that the improvement in menstrual regularity for patients receiving cyproterone compound and spironolactone was significantly higher compared to the nettle group (41). The study also showed that after the intervention, the mean hirsutism score in the participants of the nettle extract group did not differ significantly from that of the control group, and the nettle extract was as effective as COCs in reducing hormones. Although no study directly measuring the effects of nettle on hirsutism was found, a study by Najafipour and colleagues (2014), aimed at determining the impact of nettle on women with hyperandrogenism, showed that the improvement in skin conditions such as acne and oily skin was significantly greater in the group receiving the cyproterone compound and spironolactone compared to the nettle group (41).

After the intervention, most participants in both groups experienced moderate bleeding; however, there was a significant difference in the amount of bleeding between the two groups. Specifically, there were three cases of heavy bleeding in the nettle group, whereas no heavy bleeding was reported in the combined oral contraceptive group. The effect of COCs in reducing bleeding was greater than that of nettle extract. No similar study was found based on the search conducted using scientific sources.

A strength of the study was its design as a triple-blind study, with only one observer conducting all sampling stages to assess inclusion criteria and monitor the intervention, thereby preventing observer bias. However, the study has several limitations: the short duration of the intervention and the lack of evaluation of long-term effects. It did not assess the impact of different doses of nettle extract and was conducted with the lowest possible dose. Higher doses might have shown more significant effects. Additionally, confounding variables such as diet, insulin or lipid levels and exercise habits were not considered. Therefore, it is recommended that the impact of different doses of nettle extract on PCOS symptoms, potential dose-response relationships, and optimal therapeutic doses be examined. It is also recommended to investigate the possible synergistic effects of nettle extract alongside other established PCOS treatments, including metformin or lifestyle changes.

## Conclusion

The results of the research indicated that nettle extract was as effective as oral contraceptives (LD pills) in reducing levels of dehydroepiandrosterone (DHEA), total testosterone, follicle-stimulating hormone (FSH), and luteinizing hormone (LH), as well as in decreasing the hirsutism score and menstrual bleeding duration. Therefore, the use of nettle, which is an easy, inexpensive, and accessible method, can be considered an adjunctive treatment alongside other therapy. Overall, this study contributes to the body of scientific evidence related to the management of PCOS and emphasizes the importance of precise and controlled clinical trials in evaluating potential therapeutic interventions. Further research in this field is essential to address the unmet clinical needs of women with PCOS and to advance the development of evidence-based management strategies for this common endocrine disorder. The findings of this study can be utilized in educational, clinical, and research contexts.

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## Ethical statement

The study was conducted after obtaining the necessary approvals from the Research Ethics Committee of Tabriz University of Medical Sciences (TBZMED.REC.1402.113.IR) and registration in the Iranian Clinical Trial Registry (IRCT20110606006709N25). All ethical principles in human research and clinical trials were adhered to in accordance with the ethical codes of research and the principles outlined in the Helsinki Declaration. This included voluntary participation with informed written consent, the right to withdraw from the study, confidentiality of participants' identities, and the avoidance of any harm to participants.

## Conflicts of interest

The authors declare no conflicts of interest.

## Author contributions

Study conceptualization: F.M, Kh.H, M.Sh. Study design: Kh.H, A.F-Kh, M.Sh, MR.M. Data collection: F.M, P.H, MR.M. Statistical analysis: Kh.H, M.Sh, A.F-Kh. Manuscript preparation: Kh.H, M.Sh, A.F-Kh. Manuscript editing: Kh.H, M.Sh, F.M. Project administration: F.M, M.Sh, Kh.H. All authors read and approved the final version of the manuscript.

## Data availability statement

Data will be made available upon reasonable request from the corresponding author, subject to review and agreement by the research team.

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