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# EFFECTIVENESS OF CINNAMOMUM VERUM EXTRACT AND METFORMIN ON MENSTRUAL CYCLE REGULARITY AND ADVERSE EVENT PROFILE IN PATIENTS WITH POLYCYSTIC OVARY SYNDROME (PCOS)

**Herti Marni[1], Eti Yerizel[2]*, Bobby Indra Utama[3], Arni Amir[4]**
[1]Doctoral Program in Biomedical Sciences, Faculty of Medicine, Universitas Andalas, Limau Manis, Pauh, Padang, West Sumatra 25163, Indonesia
[2]Department of Biochemistry, Faculty of Medicine, Universitas Andalas, Limau Manis, Pauh, Padang, West Sumatra 25163, Indonesia
[3]Department of Obstetrics and Gynecology, Faculty of Medicine, Universitas Andalas, Limau Manis, Pauh, Padang, West Sumatra 25163, Indonesia
[4]Biomedical Sciences, Faculty of Medicine, Universitas Andalas, Limau Manis, Pauh, Padang, West Sumatra 25163, Indonesia
*ety_yerizel@yahoo.co.id

**ABSTRACT**
A Quasi-Experimental Pretest-Posttest Control Group Clinical Trial. Polycystic ovary syndrome (PCOS) is a common endocrine-metabolic disorder among reproductive-age women, with menstrual cycle disturbance as one of its principal clinical manifestations. Metformin is the standard therapy but is often limited by gastrointestinal adverse effects that reduce adherence, prompting interest in herbal alternatives such as Cinnamomum verum. This study aimed to compare the effectiveness of C. verum extract with metformin on the restoration of menstrual cycle regularity, and to compare the incidence and severity of adverse events in women with PCOS. A quasi-experimental pretest-posttest control group design involved aged 18-40 years with PCOS, allocated into two parallel groups (n=40): C. verum 1,500 mg/day and metformin 1,500 mg/day for 12 weeks. Menstrual regularity was assessed with a structured questionnaire (amenorrhea, oligomenorrhea, hypomenorrhea, eumenorrhea). Categorical data were analyzed with chi-square/Fisher's exact tests and multivariate logistic regression adjusted for age and body mass index (BMI). Baseline characteristics and initial menstrual disturbance patterns were comparable between groups. After 12 weeks, all subjects in both groups (100%) achieved eumenorrhea. Adverse events were markedly less frequent in the C. verum group (12.5%; predominantly grade 1) than in the metformin group (95.0%; predominantly grade 2 gastrointestinal complaints), $p<0.001$. Twelve-week supplementation with C. verum 1,500 mg/day is comparable to metformin in restoring menstrual cycle regularity in women with PCOS, but with a markedly lower incidence and severity of adverse events, supporting its potential as a better-tolerated therapeutic alternative.

Keywords: adverse events; cinnamomum verum; menstrual cycle; metformin; polycystic ovary syndrome

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## INTRODUCTION

Polycystic ovary syndrome (PCOS) is one of the most common endocrine-metabolic disorders among women of reproductive age, with principal clinical manifestations including ovulatory dysfunction, hyperandrogenism, and polycystic ovarian morphology (Rosenfield and Ehrmann, 2016; Deswal et al., 2020; Harada, 2022; Singh et al., 2023). The diagnosis of PCOS follows the Rotterdam (2003) criteria, which require at least two of three findings: oligo/anovulation, clinical or biochemical hyperandrogenism, and polycystic ovarian morphology on ultrasound (Christ and Cedars, 2023). One of the complaints most directly experienced by patients is disturbance of menstrual cycle regularity, ranging from secondary amenorrhea and oligomenorrhea to hypomenorrhea, which substantially affects quality of life and fertility potential.

Metformin, as an insulin sensitizer, is a widely used first-line therapy to improve insulin resistance and ovulatory dysfunction in PCOS (Sadeghi et al., 2022; Brand et al., 2025). However, its use is

often limited by gastrointestinal adverse effects such as nausea, bloating, and diarrhea, which are among the main causes of non-adherence to long-term therapy (Notaro and Neto, 2022; Saadati et al., 2025). This has driven interest in alternative therapies that are equally effective but have a more favorable safety profile.

Cinnamomum verum (true cinnamon) has been studied as a candidate complementary therapy for PCOS (Maleki et al., 2021; Manouchehri et al., 2023). Kort and Lobo (2014), in a randomized controlled trial, reported that cinnamon supplementation significantly improved menstrual cycle regularity compared with placebo. Ainehchi et al. (2020) also reported improvement in several clinical parameters among infertile women with PCOS who received an herbal mixture containing cinnamon. Earlier, Wang et al. (2007) reported that cinnamon extract reduced insulin resistance parameters in women with PCOS, and Borzoei et al. (2017, 2018) found that cinnamon supplementation improved antioxidant status, serum lipids, and metabolic factors. Dastgheib et al. (2022) further compared cinnamon, ginger, and metformin in a randomized placebo-controlled trial assessing metabolic, anthropometric, and sex hormone parameters in women with PCOS. Regarding safety, Ranasinghe et al. (2012) demonstrated that C. verum contains substantially lower coumarin levels than Cinnamomum cassia, so that the toxicity risks often attributed to other cinnamon species do not apply to it, and the European Medicines Agency (2010) has classified C. verum as an herbal substance with a well-documented safety profile for short-term use.

Most prior studies have focused on improvement of hormonal or metabolic biomarkers, whereas a direct and comprehensive comparison between a clinically pragmatic efficacy outcome that is easily observed in primary carenamely menstrual cycle regularity and the burden of adverse events remains limited. Both parameters are practically important because they require no specialized laboratory testing and directly affect patient adherence and clinical experience. This study aimed to compare the effectiveness of C. verum with metformin in restoring menstrual cycle regularity, and to compare the incidence and severity of adverse events in women with PCOS.

## METHOD

This study used a quasi-experimental pretest-posttest control group design. The study was conducted at the Obstetrics and Gynecology Polyclinic of RSIA Annisa Pekanbaru for subject recruitment and clinical assessment, supported by the Biomedical Laboratory of the Faculty of Medicine, Universitas Andalas.

### *Inclusion and Exclusion Criteria*

The study population comprised women of reproductive age (18-40 years) who were married and diagnosed with PCOS based on the Rotterdam (2003) criteria. Inclusion criteria were willingness to participate and sign informed consent, together with fulfillment of the Rotterdam criteria. Exclusion criteria included other endocrine-metabolic disorders (thyroid disease, hyperprolactinemia, diabetes mellitus, Cushing's syndrome), cardiovascular or cerebrovascular disease, hypertension, use of drugs/supplements affecting the outcome measures, smoking, regular exercise (>2 weeks), cinnamon allergy, and pregnancy or exclusive breastfeeding.

### *Treatment Group*

The treatment group received *C. verum* extract capsules 500 mg three times daily (1,500 mg/day), while the control group received metformin tablets 500 mg three times daily (1,500 mg/day), both for 12 weeks. Capsules in both groups were made identical in color, shape, size, and packaging. The independent variable was the type of intervention (*C. verum* vs. metformin). The dependent variables analyzed in this article were: (1) menstrual cycle regularity, assessed with a structured questionnaire and categorized as secondary amenorrhea (>90 days), oligomenorrhea (36-60 days or 6-8 cycles/year), hypomenorrhea (duration <2 days, volume <25 cc), and eumenorrhea (cycle 21-35

days); and (2) adverse event profile, assessed with a structured questionnaire regarding complaints occurring during or shortly after drug consumption.

### *Data Analysis*

Graded for severity using the Common Terminology Criteria for Adverse Events (CTCAE) version 6.0, published by the National Cancer Institute. Age and body mass index (BMI) were treated as covariates in the multivariate analysis. Normality of numerical data was tested using the Shapiro-Wilk test. Categorical data (menstrual cycle regularity and adverse event profile) were presented as absolute frequencies and percentages, and compared between groups using the chi-square test or Fisher's exact test as appropriate. To identify independent predictors of adverse events, multivariate logistic regression was performed with treatment group, age, and baseline BMI as independent variables. Statistical significance was set at $p<0.05$. All data analyses were performed using SPSS version 27.

### *Ethical Approval*

This study received ethical approval from the Health Research Ethics Committee of the Faculty of Medicine, Universitas Andalas, under number 517/UN.16.2/KEP-FK/2025.

## RESULT

A total of 80 subjects completed the study, equally divided between the C. verum and metformin groups (n=40 each). Baseline characteristics and initial menstrual disturbance patterns were relatively comparable between groups (Table 1).

Table 1.
Baseline Characteristics and Initial Menstrual Status of Study Subjects

| Variable | C. verum (n=40) | Metformin (n=40) |
|---|---|---|
| Age (years), mean ± SD | 28.60 ± 3.10 | 29.90 ± 3.60 |
| BMI (kg/m²), mean ± SD | 27.75 ± 5.43 | 29.18 ± 6.40 |
| Baseline menstrual status, n (%) | | |
| Secondary amenorrhea | 19 (47.5%) | 22 (55.0%) |
| Oligomenorrhea | 17 (42.5%) | 15 (37.5%) |
| Hypomenorrhea | 4 (10.0%) | 3 (7.5%) |

After 12 weeks of intervention, all subjects in both groups achieved a eumenorrheic cycle pattern, i.e., 40 subjects (100%) in the *C. verum* group and 40 subjects (100%) in the metformin group. In contrast, the adverse event profile showed a striking difference: only 5 subjects (12.5%) in the *C. verum* group reported adverse events, compared with 38 subjects (95.0%) in the metformin group (Table 2). Adverse events in the metformin group were dominated by gastrointestinal complaints (nausea, bloating, diarrhea, and dizziness), which overall corresponded to grade 2 (moderate) according to CTCAE v6.0 requiring symptomatic management but not hospitalization whereas adverse events in the *C. verum* group were all grade 1 (mild) and did not interfere with treatment continuation.

Table 2.
Menstrual Cycle Regularity and Adverse Event Profile After 12 Weeks of Intervention

| Variable | C. verum (n=40) | Metformin (n=40) | p-value |
|---|---|---|---|
| Eumenorrhea, f (%) | 40 (100%) | 40 (100%) | - |
| Adverse events – Present, f (%) | 5 (12.5%) | 38 (95.0%) | <0.001* |
| Adverse events – Absent, f (%) | 35 (87.5%) | 2 (5.0%) | |
| Severity grade (CTCAE v6.0) | Grade 1 (mild) | Grade 2 (moderate) | - |

*Chi-square/Fisher's exact test

To identify independent predictors of adverse events, multivariate logistic regression was performed with treatment group, age, and baseline BMI as independent variables (Table 3). The C. verum group showed a large negative coefficient ($B = -5.881$) with an odds ratio (OR) of 0.003 (95% CI 0.0002–0.033; $p<0.001$), indicating a much lower risk of adverse events in the C. verum group compared with metformin after adjusting for age and BMI. Age was not significantly associated

with adverse events (OR 1.165; 95% CI 0.888–1.528; p=0.269), whereas baseline BMI showed a significant negative association (OR 0.849; 95% CI 0.724–0.996; p=0.045), indicating that a higher baseline BMI was associated with a slightly lower likelihood of adverse events in this model.

## DISCUSSION

The finding that all subjects in both groups achieved eumenorrhea after 12 weeks indicates that C. verum has effectiveness comparable to metformin in restoring menstrual cycle regularity in women with PCOS. This finding is consistent with Kort and Lobo (2014), who reported a significant improvement in menstrual cycle regularity in the group receiving cinnamon supplementation compared with placebo, and with the systematic review by Wahyuningtyas and Sa'adi (2021), which concluded that cinnamon extract can improve menstrual cyclicity in women with PCOS. Mechanistically, restoration of menstrual regularity in PCOS is associated with improved insulin sensitivity, reduced intraovarian androgen levels, and normalization of the follicular environment, which together support consistent restoration of ovulation (Ainehchi et al., 2020; Armanini et al., 2022). Experimental evidence from a PCOS mouse model further supports a beneficial effect of cinnamon on ovarian function (Dou et al., 2018).

The most significant and consistent difference in this study was in the adverse event profile. The incidence of adverse events in the metformin group (95.0%) was far higher than in the C. verum group (12.5%), and multivariate logistic regression confirmed treatment type as the strongest independent predictor, even after adjusting for age and BMI. Metformin's gastrointestinal adverse effects nausea, bloating, and diarrhea are a long-recognized consequence and one of the main causes of non-adherence to PCOS therapy (Notaro & Neto, 2022; Saadati et al., 2025). In contrast, the excellent safety profile of C. verum observed in this study is consistent with the systematic review by Ranasinghe et al. (2012), which showed that true cinnamon (C. verum) contains substantially lower coumarin levels than Cinnamomum cassia, so that the toxicity risks often attributed to other cinnamon species are not relevant to C. verum, and with the European Medicines Agency (2010) assessment classifying C. verum as an herbal substance with a well-documented safety profile for short-term use.

## CONCLUSION

Twelve-week supplementation with Cinnamomum verum 1,500 mg/day has effectiveness comparable to metformin 1,500 mg/day in restoring menstrual cycle regularity in women with PCOS, with a markedly lower incidence and severity of adverse events. These findings support the potential of C. verum as a better-tolerated therapeutic alternative, particularly for patients intolerant to the gastrointestinal adverse effects of metformin.

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