9 Therapeutic Effect of Curcumin in Women with Polycystic Ovary Syndrome Receiving Metformin: A Randomized Controlled Trial

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Abstract

Polycystic ovary syndrome (PCOS) is the most common cause of anovulatory infertility, for which the insulin sensitizer metformin has been used therapeutically. It has been shown that curcumin also exhibits insulin-sensitizing properties. Given that metformin acts as an ovulation inducing agent and both curcumin and metformin can reduce insulin resistance, the aim of the current study was to evaluate the effect of metformin with and without curcumin nanomicelles in the treatment of women with polycystic ovary syndrome. This clinical trial was conducted on 100 women with PCOS, diagnosed according to the Rotterdam criteria, who were sequentially recruited and randomly divided into two groups (n = 50 each). Group 1 received 500 mg metformin three times daily and group 2 received 80 mg/day capsule of curcumin nanomicelle and 500 mg metformin three times a day for

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3 months. After collecting fasting blood samples, biochemical parameters including triglycerides, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), total cholesterol, plasma glucose, alanine amino transferase (ALT) and aspartate aminotransferase (AST) were evaluated based on enzymatic methods. Hormonal parameters were assessed using immunoassay kits. Insulin resistance (HOMA-IR) and insulin-sensitivity check index (QUICKI) were also assessed. After treatment, fasting insulin, HOMA-IR, and total testosterone in group 2 were significantly lower than those in group 1 ($p < 0.05$). Post-treatment LDL-C levels in groups 1 and 2 were 117.9 ± 24 and 91.12 ± 19.46 mg/dL, respectively ($p < 0.01$). In addition, HDL-C levels were increased with curcumin (group 1: 38.1 ± 4.36 mg/dL; group 2: 44.12 ± 7.3 mg/dL, $p < 0.05$). Total cholesterol was decreased with curcumin level (group 1: 207.9 ± 39.84 mg/dL; group 2; 159.7 ± 48.43 mg/dL, $p < 0.05$), with a decrease in triglycerides levels (group 1: 141.6 ± 9.57; group 2: 97.5 ± 8.8 mg/dL, $p < 0.01$). This study showed that curcumin has a synergistic effect with metformin in the improvement of insulin resistance and lipid profile in patients with PCOS. Therefore, the combined use of metformin and curcumin may have therapeutic utility in patients with PCOS.

Keywords

Nanomicelle curcumin · Metformin · Polycystic ovary syndrome

9.1 Introduction

Polycystic ovary syndrome (PCOS) is a heterogeneous and complex disease [1, 2] characterized by chronic anovulation, menstrual irregularity and hyperandrogenism [1], with associated infertility and metabolic disturbances including insulin resistance, glucose intolerance, hypertension, obesity [3], and dyslipidemia [1] in women of reproductive age. PCOS is a polygenic disorder influenced by genetic susceptibility and environmental risk factors. Among environmental parameters, lifestyle aspects including sedentary behavior and improper diet contribute to the pathogenesis of PCOS [3, 4].

Metformin is the most commonly used drug in the treatment of type 2 diabetes that improves the sensitivity of peripheral tissues to insulin, prevents hepatic gluconeogenesis and decreases oxidative stress. Moreover, the use of this drug decreases androgen levels and increases the levels of sex hormone binding globulin (SHBG) [1]. In addition, it improves metabolic syndrome in patients with PCOS. Therefore, the use of metformin in women with PCOS is common. However, it is associated with the side effects of abdominal pain, nausea, diarrhea, anorexia, flatulence and bloating [1].

Curcumin is an extracted polyphenol from turmeric, which is safe and endowed with numerous biological effects [5–12]. Anti-inflammatory, anti-obesity and anti-diabetic properties of curcumin are reported in some studies [13]. Curcumin exerts anti-inflammatory effects by modulating cytokines and chemokines [14–16], and it shows antioxidant activities by inhibiting reactive oxygen species and inducing an antioxidant response [17]. In addition, favorable effects of curcumin on cancers may be due to direct anti-inflammatory and anti-oxidative effects as well as its ability to modulate the immune system. Recently, some studies have reported that curcumin through reducing luteinizing hormone (LH) can induce ovulation and modulate ovarian responsiveness [18]. The effect of curcumin in diabetes is through decreasing death of pancreatic islet beta cells, preventing insulin resistance and improving beta cell function. Current research on curcumin has concentrated on nanocarrier delivery systems including nanostructured lipid carrier and nanoparticles to enhance aqueous stability, solubility and bioavailability [19]. Therefore, it seems that nanocarrier and nanomicelles can be considered as promising delivery systems for curcumin [14].

Given that insulin resistance plays an important role in the pathogenesis of PCOS [20], we hypothesized that insulin resistance would be

reduced to a greater degree with nanomicelle curcumin plus metformin in comparison to metformin alone in the treatment of women with PCOS.

9.2 Materials and Methods

9.2.1 Sample Selection

This clinical trial study was conducted on 100 women with PCOS presented sequentially to the Shahid Sadoughi Hospital- Yazd- Iran from March 2017 to March 2018 and were randomized either into one or the other clinical trial arms. All patients fulfilled the Rotterdam criteria for diagnosis with 2 out of 3 features of oligomenorrhea/amenorrhoea, clinical or biochemical hyperandrogenism (Ferriman-Gallwey score >8; free androgen index >4 respectively), and polycystic ovaries on transvaginal ultrasound (≥ 12 antral follicles in at least one ovary or ovarian volume of ≥10 cm^3) [21]. Study participants had no concurrent illness, were not on any medication for the preceding 9 months and were not planning to conceive. Non-classical 21-hydroxylase deficiency, hyperprolactinaemia, Cushing's disease and androgen-secreting tumors were excluded by appropriate tests. Written informed consent was given by each participant and the study was approved by ethics committee (IR.SSU.MEDICINE.REC.1396.195) of Shahid Sadoughi University. The study was recorded in the Iranian Registry of Clinical Trial system with number IRCT20090422001836N11. The patient flowchart in shown in Fig. 9.1.

9.2.2 Classification of Patients

Patients were randomly divided into two groups (n = 50), using a random number table. The first group received 500 mg metformin three times daily and the second group received 80 mg/day capsule of curcumin nanomicelle (Exir Nano Sina Co, Tehran, Iran) and 500 mg metformin three times daily. In each group, treatment was undertaken for 12 weeks.

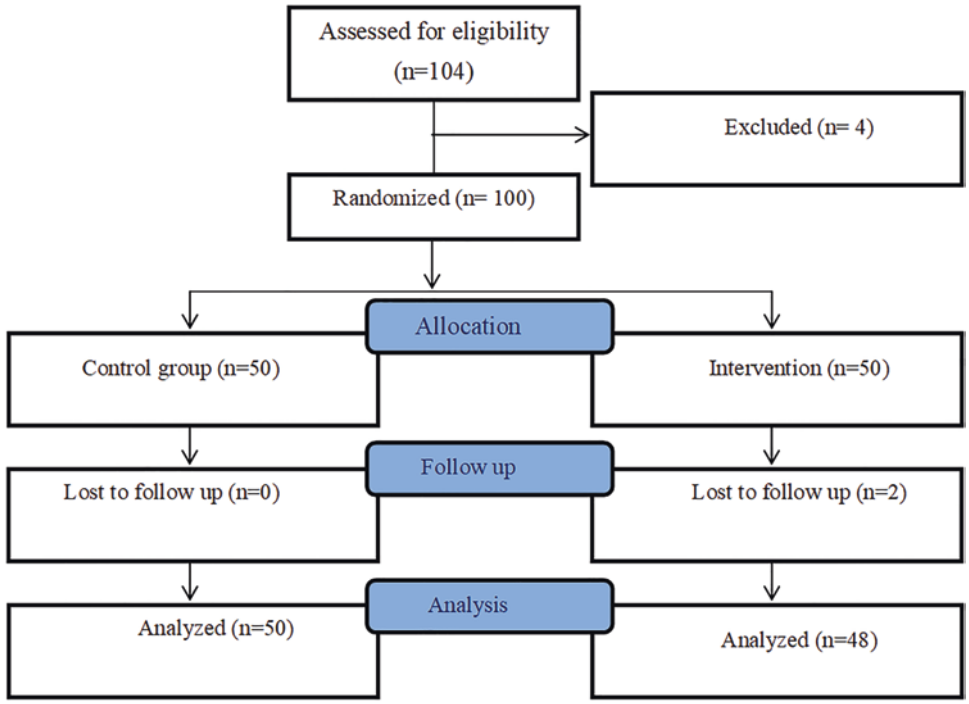

Fig. 9.1 Patient flowchart

9.2.3 Analysis of Biochemical and Hormonal Parameters

Blood samples were taken from patients after 8 h fasting. After collecting blood samples, serum was separated by centrifugation at 1000 x g for 1 min and frozen at −20 °C for subsequent analyses. Biochemical parameters including fast blood sugar, cholesterol, low density lipoprotein (LDL), high density lipoprotein (HDL), triglycerides, alanine aminotransferase (ALT), and aspartate aminotransferase (AAT) were assessed based on an enzymatic method (Pars Azmoon kit, Tehran, Iran) using a BT-3000 PLUS analyzer. Fasting serum insulin was evaluated by an enzyme-linked immunoadsorbent assay (ELISA) kit (Insulin AccuLite CLIA Kit, Monobind Inc., Lake Forest, CA, USA). TSH was measured based on immunoassay method using an ELISA kit (Padtan Gostar kit, Iran) and Prolactin (PRL) was measured using a PRL assay kit (Padyab Teb kit, Tehran, Iran). Dehydroepiandrosterone (DHEAS) was also measured using an ELISA method *(DEMEDITEC Diagnostics* GmbH, Kiel, Germany). An ELISA kit was used for measuring serum level of LH and testosterone according to Pidgin Teb kit protocol, and follicle stimulating hormone (FSH) was measured according to the Padyab kit protocol. The homeostatic model assessment (HOMA) for quantify insulin resistance (IR) was calculated using the formula:

$$\text{HOMA}-\text{IR}=\begin{bmatrix}\text{fasting glucose}(\text{nmol}/\text{L})\times\\ \text{fasting insulin}(\mu U/\text{mL})/22.5\end{bmatrix}$$

The quantitative insulin-sensitivity check index (QUICKI) was assessed based on following formula:

$$1/\begin{pmatrix}\log(\text{fasting insulin}\,\mu U/\text{mL})+\\ \log(\text{fasting glucose}\,\text{mg}/\text{dL})\end{pmatrix}$$

Data including weight, body mass index (BMI), age and gender were extracted from the medical records.

9.2.4 Statistical Analysis

Sample size was calculated using a statistical power of 80%, an α value of 0.05, and a difference in means of insulin levels between intervention and control groups (11μU/mL) [22]. Data trends were visually evaluated for each androgen and non-parametric tests were applied on data that violated the assumptions of normality when analyzed using the Kolmogorov-Smirnov Test. Significance was defined at $\alpha = 0.05$. All analyses were conducted using IBM-SPSS version 17.0.

9.3 Results

In this study, the age range of patients was 18–40 years old. The mean ages of patients in the two groups did not differ (28.8 ± 2.44 and 29.2 ± 2 years old, respectively). Comparison of biochemical parameters in two groups before treatment is shown in Table 9.1. This revealed no significant difference between the two groups for any of the biochemical parameters before treatment. Table 9.2 shows the between group effect of metformin and metformin/curcumin on biochemical parameters after 3 months treatment. This shows that significant differences were seen between two groups for fasting insulin, HOMA-IR, LDL, HDL, total cholesterol, triglycerides and testosterone ($p < 0.05$).

Table 9.3 shows the within group comparison of biochemical parameters before and after treatment with metformin alone or curcumin with metformin. Significant differences were seen before and after treatment with metformin, in terms of fasting glucose, fasting insulin, HOMA-IR, QUICKI, fasting glucose/insulin (G/I) ratio, ALT, AST, testosterone, LH and the LH/FSH ratio ($p < 0.05$). In addition, significant differences were seen before and after treatment of metformin/curcumin, regarding fasting glucose, fasting insulin, HOMA-IR, QUICKI, fasting G/I ratio, cholesterol, triglyceride, LDL, HDL, total testosterone, LH, LH/FSH ratio, AST and ALT ($p < 0.05$).

Table 9.1 Comparison of biochemical parameters in two groups before treatment

Characteristics	Metformin (group 1) N = 50	Metformin/curcumin (group 2) N = 48	p-value (ANOVA)
Age	28.8 ± 2.46	29 ± 2	0.36
Weight (kg)	73 ± 5	73.7 ± 4.6	0.48
BMI (kg/m^2)	27.01 ± 1.65	27.2 ± 2.2	0.26
Fasting glucose (mg/dL)	107.86 ± 7	110.36 ± 5.6	0.054
Fasting insulin (μU/mL)	18.1 ± 2.7	18 ± 2.8	0.86
HOMA-IR	4.16 ± 1.42	4.36 ± 0.72	0.52
QUICKI	0.31 ± 0.01	0.3 ± 0.01	0.91
Fasting G/I (mg/dL per μIU/mL)	8.4 ± 5.56	8.6 ± 5. 1	0.11
LDL cholesterol (mg/dL)	119.28 ± 23.5	114.04 ± 24.6	0.28
HDL cholesterol (mg/dL)	37.2 ± 5.2	33.1 ± 6.1	0.76
Serum cholesterol (mg/dL)	215.1 ± 37.2	200.3 ± 31.4	0.83
Serum triglyceride (mg/dL)	143 ± 8.3	129.5 ± 5.7	0.43
DHEAS (μg/dL)	180 ± 4.4	191 ± 11.1	0.69
Total testosterone (μg/L)	0.7 ± 0.14	0.74 ± 0.18	0.4
FSH (IU/L)	5.9 ± 3.2	5.4 ± 4.2	0.34
LH (IU/L)	7.6 ± 2.9	7.9 ± 1.9	0.39
LH/FSH	1.7 ± 0.92	1.7 ± 1.5	0.72

BMI body mass index, *HOMA-IR* homeostatic model assessment of insulin resistance, *QUICKI* quantitative insulin check index, *G/I* glucose/insulin, *LDL* low density lipoprotein, *HDL* high density lipoprotein, *DHEAS* dehydroepiandrosterone sulfate, *FSH* follicle-stimulating hormone, *LH* luteinizing hormone

Table 9.2 The effect of metformin and metformin/curcumin on biochemical parameters between groups after treatment

Characteristics	Metformin group N = 50 Post treatment	Metformin/curcumin N = 48 Post treatment	p- value (ANOVA)
Weight (kg)	72.6 ± 4.7	73.3 ± 4	NS
BMI (kg/m^2)	26.81 ± 1.82	26.37 ± 3.7	NS
FPG (mg/dL)	94.26 ± 8.4	95.32 ± 9	NS
Fasting insulin (μU/mL)	13.75 ± 3	12.5 ± 3.4	<0.05
HOMA-IR	2.83 ± 0.65	2.57 ± 0.76	<0.05
Testosterone (μg/L)	0.62 ± 0.12	0.4 ± 0.16	0.035
DHEAS (μg/dL)	175 ± 43	189.3 ± 10.67	NS
QUICKI	0.32 ± 0.02	0.32 ± 0.03	NS
Fasting G/I ratio (mg/dL per μIU / mL)	13.9 ± 10.32	14.73 ± 6.4	0.058
LDL cholesterol (mg/dL)	117.9 ± 24	91.12 ± 19.46	<0.01
HDL cholesterol (mg/dL)	38.1 ± 4.36	44.12 ± 7.3	<0.05
Serum cholesterol (mg/dL)	207.9 ± 39.84	159.7 ± 48.43	<0.01
Serum triglyceride (mg/dL)	141.6 ± 9.57	97.5 ± 8.8	<0.01
FSH (IU/L)	6.2 ± 2.8	5.8 ± 3.8	NS
LH(IU/L)	6.4 ± 2.6	6.3 ± 1.7	NS
LH/FSH	1.1 ± 0.78	1.1 ± 0.65	NS

BMI body mass index, *FPG* fasting plasma glucose, *HOMA-IR* homeostatic model assessment of insulin resistance, *QUICKI* quantitative insulin check index, *LDL* low density lipoprotein, *HDL* high density lipoprotein, *DHEAS* dehydroepiandrosterone sulfate, *FSH* follicle-Stimulating hormone, *LH* luteinizing hormone

Table 9.3 Comparison of biochemical parameters before and after treatment in two groups

Variable	Metformin treatment (group 1)			Metformin/curcumin treatment (group 2)		
	Pretreatment	Post treatment	p- value	Pretreatment	Post treatment	p- value
Weight (kg)	73 ± 5	72.6 ± 4.7	NS	73.7 ± 4.6	73.3 ± 4	NS
BMI (kg/m^2)	27.01 ± 1.65	26.81 ± 1.82	NS	27.2 ± 2.2	26.37 ± 3.7	NS
FPG (mg/dl)	107.86 ± 7	94.26 ± 8.4	0.008	110.36 ± 5.6	95.32 ± 9	0.003
Fasting insulin (μU/mL)	18.1 ± 2.7	13.75 ± 3	0.004	18 ± 2.8	12.5 ± 3.4	<0.001
HOMA-IR	4.16 ± 1.42	2.83 ± 0.65	0.001	4.36 ± 0.72	2.57 ± 0.76	0.0013
QUICKI	0.31 ± 0.01	0.32 ± 0.02	0.009	0.3 ± 0.01	0.32 ± 0.03	0.006
Fasting G/I (mg/dL per μIU/mL)	8.4 ± 5.56	13.9 ± 10.32	<0.05	8.6 ± 5. 1	14.73 ± 6.4	<0.01
LDL cholesterol (mg/dL)	119.28 ± 23.5	117.9 ± 24	NS	114.04 ± 24.6	91.12 ± 19.46	<0.001
HDL cholesterol (mg/dL)	37.2 ± 5.2	38.1 ± 4.36	NS	33.1 ± 6.1	44.12 ± 7.3	<0.01
Serum cholesterol (mg/dL)	215.1 ± 37.2	207.9 ± 39.84	NS	200.3 ± 31.4	159.7 ± 48.43	>0.001
Serum triglyceride (mg/dL)	143 ± 8.3	141.6 ± 9.57	NS	129.5 ± 5.7	97.5 ± 8.8	>0.01
DHEAS (μg/dL)	180 ± 44	175 ± 43	NS	191 ± 11.1	189.3 ± 10.67	NS
Total testosterone (μg/L)	0.7 ± 0.14	0.62 ± 0.12	0.003	0.74 ± 0.18	0.4 ± 0.16	>0.001
FSH (IU/L)	5.9 ± 3.2	6.2 ± 2.8	NS	5.4 ± 4.2	5.8 ± 3.8	NS
LH(IU/L)	7.6 ± 2.9	6.4 ± 2.6	>0.01	7.9 ± 1.9	6.3 ± 1.7	>0.01
LH/FSH	1.7 ± 0.92	1.1 ± 0.78	>0.01	1.7 ± 1.5	1.1 ± 0.65	>0.01
AST	31 ± 7.48	27.54 ± 6.57	0.017	29.5 ± 6.84	21 ± 6.0	>0.01
ALT	37.16 ± 10.8	32.98 ± 10.3	0.049	38.26 ± 9.45	23.28 ± 7.89	<0.01

FPG fasting plasma glucose, *HOMA-IR* Homeostatic model assessment of insulin resistance, *QUICKI* quantitative insulin check index, *HDL* High density lipoprotein, *DHEAS* Dehydroepiandrosterone sulfate, *LDL* low density lipoprotein, *FSH* follicle-stimulating hormone, *AST* aspartate aminotransferase, *LH* luteinizing hormone, *ALT* alanine aminotransferase, *NS* non- significant

9.4 Discussion

This study showed a significant reduction in fasting insulin and HOMA-IR after metformin plus curcumin treatment in women with PCOS. Aguilar et al. evaluated the effect of curcumin supplementation on insulin sensitivity and observed that curcumin consumption decreased insulin resistance and improved glucose tolerance [23], which is consistent with our findings. Additionally, Rahimi et al. observed decreased fasting plasma glucose following the administration of nano-curcumin in diabetic patients [24]. Ameli et al. reported that curcumin improves insulin secretion via reducing plasma glucose in diabetic rats [25]. Another study showed that curcumin improved glucose metabolism by activation of adenosine monophosphate (AMP) kinase in the liver and induced glucose transporter-4 (GLUT-4) expression leading to increased peripheral glucose uptake [26]. Furthermore, it was revealed that curcumin reduced glucose levels and increased insulin secretion through peroxisome proliferator-activated receptor (PPAR)-γ activation [27, 28], explaining the hypoglycemic effects of this natural agent.

In our study, curcumin therapy increased FSH levels and decreased LH, DHEAS, and testosterone concentrations in patients with PCOS. Mohammadi et al. found increased levels of FSH and decreased LH and testosterone concentrations following curcumin treatment in a model of PCOS [1], which is consistent with our results. These effects may be because curcumin inhibits tumor necrosis factor (TNF)-α, interleukin (IL)-6, and C-reactive protein expression, improving ovulation and the corpus luteum [1]. This suggests that this polyphenol could improve the reproductive endocrine function and induce follicular development. However, this study was not designed to look at this specifically. Nabiuni et al. demonstrated that curcumin treatment resulted in improvement of PCOS symptoms and initiation of ovulation via antioxidant and anti-inflammatory effects [18]. Other studies have shown that curcumin induces apoptosis, inhibits

pituitary tumor cell proliferation, and reduces the production and release of LH [29].

Yan et al. found that curcumin treatment mitigates oxidative stress, apoptosis, and ovarian injury through regulation of nuclear factor erythroid 2-related factor 2/heme oxygenase-1 (Nrf2/HO-1) and phosphatidylinositol 3-kinase/protein kinase B (PI3K/Akt) signaling pathways in mice with induced ovarian failure [30]. Consistent with this, Melekoglu et al. observed that curcumin administration ameliorated ovarian failure by decreasing oxidative stress markers, FSH and LH levels, and improving histophatological parameters [31], suggesting a protective effect of this natural compound against ovarian failure. It is important to note that although the intervention period of our study was too short to demonstrate the regularization of menstrual cycle, the benefits of curcumin on PCOS symptoms and hormonal levels may reflect an amelioration in menstrual and ovulatory cycles. Therefore, longer clinical trials are needed in order to corroborate the potential clinical impact of curcumin on menstrual disorders and endocrine dysfunction.

Beneficial effects of curcumin plus metformin were seen on lipid parameters by a reduction in total cholesterol, LDL, triglycerides, and increased HDL levels. In accordance with our findings, others have reported a significant decrease in total cholesterol, LDL, and triglyceride concentrations after curcumin therapy [32, 38]. These lipid-lowering effects of curcumin could be explained by a number of possible mechanisms, such as increased activity of lipoprotein lipase and fatty acid β-oxidation, and inhibition of 3-hydroxy-3-methylglutaryl coenzyme A reductase, fatty acid synthase, and acyl coenzyme A cholesterol acyltransferase [33]. Moreover, a previous meta-analysis revealed that curcumin supplementation significantly decreased plasma concentrations of triglycerides and increased HDL levels [34], which is also consistent with our study. This potential cardioprotective action of curcumin could be explained through an increase in lipoprotein lipase activity and hydrolysis of triglyceride-rich lipoproteins, causing reduced circulating triglyceride levels [35]. Also, curcumin may ameliorate HDL function by regulating apolipoprotein-AI, cholesteryl ester transfer protein (CETP), lecithin–cholesterol acyltransferase (LCAT), serum paraoxonase/arylesterase 1 (PON1), and myeloperoxidase (MPO) activities [36]. It is well-known that atherogenic dyslipidemia, characterized by elevated triglycerides and low HDL concentrations, is a central therapeutic target in patients with cardiovascular disease due to the high residual risk of cardiovascular events and microvascular complications [37]. Because curcumin showed a combined effect by raising HDL levels and decreasing triglycerides, this natural compound might be considered as an additional therapeutic option in the treatment of atherosclerotic cardiovascular disease.

Limitations of this study include that the treatment period was short to assess menstrual frequency and ovulatory cycles. However, 3 months were sufficient to found significant effects of curcumin administration on metabolic parameters. Secondly, although our study was not blinded and did not use a placebo, randomization would have minimized this potential source of bias.

The main strength of our study was the sample size which conferred adequate statistical power to support the efficacy of curcumin treatment in PCOS.

9.5 Conclusions

This study suggests that the nanomicellar curcumin exerts a synergistic effect with metformin in the improvement of insulin resistance and the lipid profile in patients with PCOS. Therefore, combined use of metformin and nanomicelle curcumin may be a promising alternative therapy for the treatment of PCOS. However, the clinical benefits of curcumin on menstrual disorders remain to be determined in clinical trials of longer duration.

Conflict of Interests None.

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