



Comparison of the Effect of Fenugreek and Metformin on Clinical and Metabolic Status of Cases with Polycystic Ovary Syndrome: A Randomized Trial

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Abstract

Background: It is hypothesized that fenugreek seeds are a rich source of fiber with anti-diabetic effects, which can help to lower blood glucose in patients with polycystic ovary syndrome (PCOS). In this study, the clinical and metabolic effects of fenugreek were compared to those of metformin in women with PCOS aged 16-40 years. **Methods:** In a randomized, triple-blind, parallel clinical trial, the efficacy of fenugreek 333 mg (n=55) was compared with metformin 500 mg (n=55), both administered three times a day in women with PCOS of reproductive age. Changes in some clinical outcomes and metabolic laboratory profile outcomes were evaluated at baseline and two months after the study.

Results: By the end of the intervention period, all investigated factors improved significantly in patients of both groups ($p < 0.05$). Reduction in biometric indices (body mass index and waist-hip ratio), fasting blood sugar (FBS), and insulin resistance was significantly higher after metformin consumption ($p < 0.001$). Metformin also significantly improved irregular menstruation ($p = 0.02$). In contrast, fenugreek significantly improved patients' lipid profiles, including low-density lipoprotein (LDL), high-density lipoprotein (HDL), and triglyceride (TG) compared to metformin ($p < 0.001$). Both interventions improved the patient's hair loss and hirsutism.

Conclusion: Fenugreek cannot substitute metformin in PCOS treatment. However, regarding its lipid-lowering ability and low frequency of adverse effects, it can be used as an adjuvant treatment in PCOS, especially in PCOS patients with hyperlipidemia and severe hair loss.

Keywords: Cholesterol, Fenugreek, Herbal medicine, Polycystic ovary syndrome, Randomized clinical trial, Triglyceride, Trigonella.

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Introduction

Polycystic ovary syndrome (PCOS), also called Stein-Leventhal syndrome or chronic oligoanovulation, is the most common endocrine disorder that happens during the reproductive years, causing endocrine imbalance and de-

creased infertility in women aged 15-44 years (1). PCOS causes an imbalance in sex hormones leading to growth of immature oocytes and consequently failure in ovulation (2, 3). Some of the most common symptoms of PCOS include acne,

thinning hair on the head, weight gain, irregular periods, ovarian cysts, increased skin tags, depression, and infertility (4). Insulin resistance, obesity, and lipid metabolism disorders are primarily found in women with PCOS. Insulin resistance and hyperinsulinemia are supposed to play a significant role in the pathogenesis of PCOS (5, 6). Hyperinsulinemia, characterized by abnormally high levels of insulin in circulation, increases the likelihood of abnormal ovarian androgen secretion, which can lead to the development of abnormal follicles, irregular menstruation, and ovarian insufficiency (1).

As the first-choice treatment for reproductive disorders caused by PCOS, metformin has been proven to improve insulin sensitivity, decrease hepatic glucose production, regulate intestinal glucose absorption, and directly affect ovarian steroidogenesis in granulosa cell cultures (4). In clinical settings, these pharmacological effects can lead to weight loss (7), promote menstrual regularity, and improve hirsutism (8). On the other hand, there is a growing global interest in herbal and other forms of complementary medicine approaches in recent years (9). Fenugreek seed as an herbal drug has been found to have anti-diabetic and hypocholesterolemic effects in both animal and human trials (9-12). Although numerous herbs have been approved to have anti-diabetic activity, many studies suggest that fenugreek seeds perform well in terms of safety and effectiveness (13). Furthermore, the seeds are a rich fiber source and can help lower blood glucose in patients with diabetes (14). However, few studies evaluated the clinical and metabolic effects of these medications. In this study, the clinical and metabolic effects of metformin versus fenugreek were evaluated among women with PCOS.

Methods

Study design, setting, and participants: The trial was a triple-blind, parallel study on patients with PCOS. It was performed in a gynecology department of a university affiliated hospital in Tehran, Iran, between March 2021 and February 2022. The research protocol of the study was reviewed and approved by Iran University of Medical Sciences ethics committee under the code IR.IUMS.FMD.REC.1399.552. The study was also registered in the Iranian Registry of Clinical Trials with the identification code IRCT 202201300538-74N1. All participants in this study provided writ-

ten informed consent after being fully informed about the trial.

Participants were 16-40 year old women with PCOS diagnosed based on the Rotterdam criteria (15) for at least 12 months and referred to the clinic for their menstrual problems or other hyperandrogenism symptoms including acne, hirsutism, and truncal obesity. The inclusion criteria were defined as the presence of at least two of the following conditions: disrupted ovulatory function with chronic oligomenorrhea (cycle length >35 days) or amenorrhea (cycle length >12 weeks); clinical or biochemical signs of hyperandrogenism and polycystic ovaries in the ultrasonographic view; no other disorders associated with overproduction of androgens; and fasting blood sugar (FBS) less than 126 mg/dL and normal liver and kidney function (serum creatinine less than 1.4 mg/dL). The diagnosis should also be accompanied by excluding other chronic diseases, including hyperprolactinemia, congenital adrenal hyperplasia (CAH), Cushing's syndrome, androgen-producing tumors or acromegaly, congestive heart failure, digestive problems, thyroid disorders, insulin-dependent diabetes (type 1), and type 2 diabetes (16). Candidate patients for assisted reproductive technology (ART) and those using any hormones to induce menstruation (except progesterone), antiandrogens, and blood sugar control drugs were excluded from the study.

Randomization: Patients were randomly allocated into two groups according to a randomization list generated by the online software available at: <https://www.sealedenvelope.com>. A balanced permuted block design with a block size of 4 was used to generate the randomization list. For allocation concealment, the type of intervention (A or B) was written on paper and put in a black sealed box. Both drugs (fenugreek and metformin) were placed in boxes A and B, and only the principal investigator was aware of the drug content in each group. Along with every patient who entered the study, a sealed box was picked, drugs were given to the participant, and the numbering was done by a third person and noted in the patient's case report form (CRF).

In this way, neither the outcome assessors nor the patients knew the prescribed medication. Additionally, the study data were coded as groups A and B to ensure the data analyzer remained blinded to the treatment assignments.

Procedures: For patients in the control group, metformin (Aryadaru Pharmaceutical Co, Iran) was prescribed according to the regimen used for patients with polycystic ovary syndrome (500 mg three times a day) and the intervention group received fenugreek capsules of 333 mg (KayDaru Health Technology company Iran) three times a day. Mootta capsules consist of 333 mg of dry fenugreek extract, standardized to contain 53.7% trigonelline, which is the key phytochemical compound in fenugreek. Alongside the aforementioned interventions, patients in both groups were advised to incorporate lifestyle modifications such as exercise, dietary changes, and cessation of unhealthy habits.

After fasting for 12 hr, a blood sample was taken from patients to measure the following items: fasting blood sugar and fasting insulin to calculate the homeostasis model assessment (HOMA) (17, 18) through the glucose oxidase method (Bayer Advia 1650 chemistry system); lipid profile including TG, HDL, LDL and total cholesterol by photometry and turbidimetric method using Fully Automatic device (Mindray BS380); and hormones including free testosterone, luteinizing hormone (LH), dehydroepiandrosterone-sulphate (DHEAS), 17-hydroxyprogesterone (17-OHP), prolactin in the follicular phase of the menstrual cycle, and thyroid-stimulating hormone (TSH) by electrochemiluminescence (ESL) method using fully automated assay (Immulite; DPL, USA).

Weight was measured with minimal clothing and using a digital scale with an accuracy of 1.0 kg. To measure height accurately, a tape measure with an accuracy of 1.0 cm was used. Body mass index (BMI) was then calculated using the measured weight and height. Then, the BMI was obtained by dividing an adults' weight in kilograms by their height in meters squared. Waist circumference (WC) was measured midway between the lower rib and the iliac crest on the midaxillary line, while hip circumference was measured at the level of the widest circumference over the greater trochanters. The severity of hirsutism was evaluated using the modified Ferriman-Gallwey scoring method (19), which evaluates the hair growth in nine areas, including the upper lip, chin, chest, upper abdomen, lower abdomen, upper back, arms, thighs, and lower back. The presence of polycystic ovaries was detected through abdominal ultrasound for virgin patients using Philips Affiniti 70 device and 3.5 MHz Convex probe. In comparison, for non-virgin patients, a vaginal ultrasound

using Philips Affiniti 70 device and 6.5 MHz Endocavity probe was utilized.

Outcomes: The study's primary outcomes were biometric indices and clinical symptoms of the disease including changes in hirsutism, menstrual status, and hair loss. After two months from the start of treatment, weight, waist to hip circumference, lipid profile, menstrual pattern, and hormone levels were measured again for the patients and compared with the measurements on their first visit. Patients were also asked about the occurrence of any side effects of medications including nausea, vomiting, diarrhea, hypoglycemia, headache, dizziness, and/or allergic reactions. To ensure patient compliance with drug treatment, all study participants were thoroughly informed about the importance of strictly following metformin instructions and refraining from taking other medicines during the treatment period.

Statistical analysis: The sample size was calculated using PASS 2021 software. The calculations were based on the equivalency hypothesis for BMI, with an upper equivalency ratio of 1.15 and a variation coefficient of 0.25, considering type one error of 0.05 and type two error of 0.2.

All data was collected throughout the 60-day trial and reported as mean±standard deviation (SD) and frequency (percentage). To compare continuous and categorical variables between the two groups, independent t-test and Chi-square test were applied, respectively. A similar comparison was performed using paired t-test and McNemar test to compare changes within groups before and after the intervention. SPSS software version 18.0 (SPSS Inc. USA) was used for statistical analysis. The significance level of 0.05 was considered in all analyses. The analysis was conducted using a per-protocol approach.

Results

Between March 2021 to February 2022, 152 patients were screened for the inclusion and exclusion criteria. After excluding 34 patients in the initial assessment, 118 patients were randomized into two groups. Three patients in fenugreek and five in the metformin group withdrew or deviated from the protocol and were excluded from the analysis. Final per-protocol analysis was performed on two groups with the size of 55 (Figure 1).

There were no significant differences between the two groups in baseline characteristics (Table 1), demonstrating a good function of randomiza-

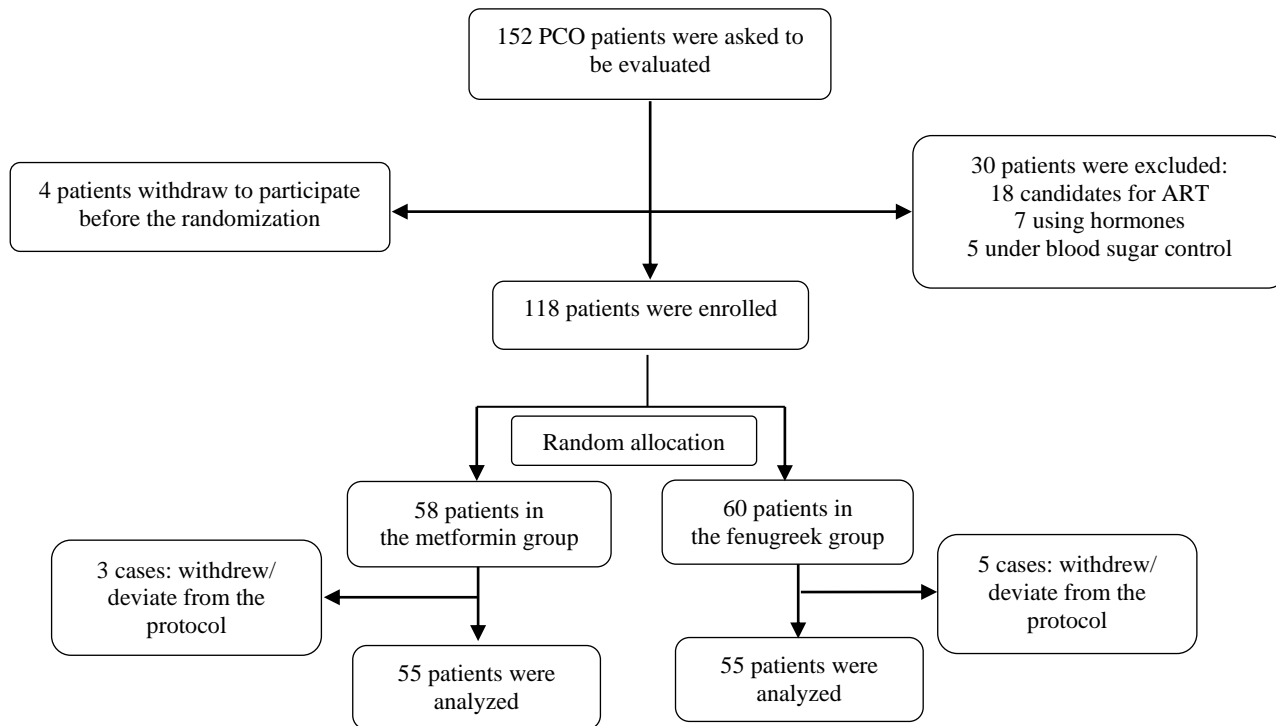


Figure 1. Participants flow diagram

Table 1. Baseline characteristics of metformin and fenugreek group

Characteristics	Metformin	Fenugreek	p-value
Age * (years)	25.5 (6.4)	27.7 (7.1)	0.12
Married	28 (50.9)	29 (52.7)	0.82
BMI (kg/m ²)	27.6 (3.5)	27.9 (3.3)	0.68
Waist to hip circumference ratio	0.8 (0.02)	0.8 (0.02)	0.30
FBS (mg/dL)	91.9 (12.4)	90.9 (10.8)	0.65
Insulin resistance **	1.6 (0.7)	1.6 (0.5)	0.43
Total cholesterol (mg/dL)	182.9 (14.5)	181.7 (10.2)	0.61
DHEAS (μmol/L)	3.6 (1.5)	3.5 (1.61)	0.43
Hirsutism score ***	11.1 (2.10)	10.6 (2.3)	0.25
Irregular menstruation	51 (92.7)	50 (90.9)	0.72

*n (n%) for numerical variables and Mean (SD) for categorical variables. ** Estimated using HOMA-IR. ***Estimated by modified Ferriman-Gallwey score

tion. The mean age in the metformin group was 25.5±6.4, and it was 27.7±7 in the fenugreek group. There were no remarkable differences between the two groups' demographic, biometric, clinical, and para-clinical features.

All biometric indices, including weight, BMI, and WHR were improved significantly after intervention (p<0.001) in both groups (Table Supplementary 1). However, the group receiving metformin exhibited greater reductions in weight and BMI compared to the fenugreek group (Table 2).

The mean±standard deviation of the laboratory profile scores of the two groups of patients and their changes after the intervention are shown in table 2 and supplementary 2. A significant decrease in cholesterol, HDL, LDL, and TG was observed between the two groups at the endpoint (week 8, p<0.05). As the data reveals, after the intervention, lipid profile improvement was significantly greater in the fenugreek group (Table 2).

Assessment of endocrine profiles of patients in-

Table 2. Comparative Analysis of Outcome Differences (Post-Intervention-Pre-Intervention)

	Fenugreek Mean (SD) n=55	Metformin: Mean (SD) n=55	p-value *
Biometric indices			
Weight (Kg)	-1.8 (0.4)	-3.0 (0.4)	<0.001
BMI (Kg/M ²)	-0.6 (0.2)	-1.1 (0.1)	<0.001
WHR	0 (0.0)	0 (0.0)	0.874
Lipid profile measures			
Cholesterol (mg/dL)	-16.8 (1.7)	-10.8 (1.1)	<0.001
HDL (mg/dL)	6.0 (2.2)	2 (0.9)	<0.001
LDL (mg/dL)	-15.3 (1.40)	-13.1 (1.8)	<0.001
TG (mg/dL)	-18.9 (1.8)	-14.0 (1.7)	<0.001
Endocrine profile measures			
Testosterone (nmol/L)	-0.05 (0.3)	-0.1 (0.3)	0.495
DHEAS (μmol/L)	-0.2 (0.3)	-0.2 (0.1)	0.857
LH (IU/ml)	-0.09 (0.12)	-0.06 (0.1)	0.084
Hydroxyprogesterone (nmol/L)	-0.2 (0.1)	-0.2 (0.1)	0.791
Prolactin (425 μg/L)	-19.3 (12.5)	-10.8 (16.8)	0.003
Hirsutism score	-0.6 (0.6)	-0.6 (0.6)	0.319
TSH (mIU/ml)	0.0 (0.1)	0.0 (0.2)	0.327
Glycemic measures			
FBS (mg/dL)	-3.8 (0.7)	-9.04 (2.4)	<0.001
Insulin resistance (HOMA-IR)	-0.2 (0.1)	-0.5 (0.2)	<0.001

* Compared between two study groups by independent t test

cluding free testosterone, DHEAS, hydroxyprogesterone, prolactin, and LH revealed that after the intervention, the hormones' levels decreased significantly in both groups (p<0.001). The serum level changes of testosterone, DHEAS, LH, and hydroxyprogesterone following the intervention were comparable across the two study groups (Table 2), although a significant decrease of prolactin was observed in the fenugreek group. While the TSH level exhibited a significant change during the study period in the fenugreek group (p=0.003), there were no statistically significant differences in the mean changes of TSH levels between the two study groups.

Finally, before the intervention, the fasting blood sugar level of patients in the fenugreek group showed an average of 90.8 mg/dl, which significantly decreased and reached 87 mg/dl after the intervention (p<0.001). With a relatively similar direction, in the metformin group, fasting blood

sugar decreased significantly from 91.9 mg/dl before intervention and reached 82.8 mg/dl after the intervention (p<0.001). Although there was no statistically significant difference between the two groups in terms of FBS before the intervention, the mean change in this measure during the intervention was significantly higher in the metformin group after the intervention (p<0.001). Study results also showed that patients' insulin resistance in both groups significantly decreased after the treatment period (p<0.001). However, this reduction was significantly higher in the metformin group (p<0.001).

More than 90% of patients had menstrual irregularities at baseline (90.9% in fenugreek and 92.7% in metformin group). Evaluation of the menstrual patterns in patients after the intervention showed that metformin significantly improved the regularity of patients' menstrual cycles (p=0.001, McNemar odds ratio=8.5). In contrast, the menstrual

Table 3. Menstrual status and hair loss before and after intervention

		After intervention								
		Fenugreek				Metformin				
		Yes	No	p-value *	Odds ratio *	Yes	No	p-value *	Odds ratio *	
Before intervention	Irregular menstruation	Yes	43	7	0.344	2.33	34	17	0.001	8.5
		No	3	2			2	2		
	Moderate to severe hair loss	Yes	16	28	<0.001	9.33	30	16	0.027	3.2
		No	3	8			5	4		

* Changes in categorical variables were evaluated using McNemar test

regularity did not significantly improve after the fenugreek intervention (Table 3). Furthermore, data revealed a significant reduction in patients' hair loss both in fenugreek ($p=0.001$, McNemar odds ratio=9.33) and metformin groups ($p=0.027$, McNemar odds ratio=3.2) (Table 3).

Evaluation of patients for adverse drug reactions showed that 58.2% of patients taking metformin experienced nausea, and 29.1% reported headaches. On the other hand, among those who used fenugreek, 10.9% experienced nausea. There was no other adverse drug reaction, including abdominal pain, allergic reaction, hypoglycemia, dizziness, and diarrhea.

Discussion

Polycystic ovary syndrome is a prevalent endocrine system disorder in women of reproductive age. Absence of menstruation or irregular menstruation in adolescents results in serious mental and emotional distress, loss of self-confidence, and anxiety. Furthermore, PCOS has been proven to be significantly associated with metabolic disorders with a prevalence of insulin resistance in 50-70% of individuals and up to 70% for dyslipidemia (20, 21). It has been shown that a high-fat diet induces obesity and is linked with PCOS (22). Sarray et al. showed that the adiponectin/leptin and adiponectin/resistin ratios present novel predictor indices for PCOS (23). In another study by Ezeh et al., findings revealed that women with PCOS showed unfavorable body composition characterized by increased total body fat relative to lean mass (higher fat-to-lean mass ratio) compared to BMI-matched controls (24). Ranasinha et al. affirmed the findings and concluded that women with PCOS were more likely to present with metabolic syndrome compared to age- and BMI-

matched controls. They added that obesity and insulin resistance were strongly associated with metabolic disorder in those suffering from PCOS (25). In line with our study, Al-Habori and Raman showed that fenugreek improved glucose tolerance primarily by increasing plasma insulin levels (26). The results of Gupta et al.'s study revealed that in the treatment group (who received 1 gram of fenugreek seed hydroalcoholic extract per day) compared to the control group (who received a placebo capsule and usual care), insulin level was significantly lower. In fact, the treatment group showed a significant decrease in insulin resistance and an increase in beta cell secretion, ultimately leading to higher insulin sensitivity, which is beneficial to health (27). According to Puri et al., the treatment with the extract of fenugreek seeds significantly improves glucose tolerance and insulin response through augmenting insulin secretion (28). Correspondingly, Basch et al. highlighted that the use of fenugreek seed extract produces two intestinal enzymes that play a key role in the metabolism of carbohydrates and the reduction of blood sugar levels through inhibiting the activity of alpha-amylase and sucrase (29).

Several treatment regimens including metformin, cabergoline, myo-inositol, D-chiro-inositol, and combined oral contraceptives such as estradiol and/or non-androgenic progesterone, and aromatase inhibitors have been widely used for PCOS (30-32). Positive short-term and long-term effects have been documented for these PCOS treatments (33-35).

There has been a considerable increase in use of alternative therapeutic approaches in recent years. Several herbal products have shown promising results for PCOS patients (36). Our present study found that fenugreek seeds extract therapy in

comparison with metformin improved menstrual regularity and ovulation function in PCOS women and the results were in agreement with the reported finding of Azziz et al. (2). Indeed, the major compounds in fenugreek seed oil including linoleic acid reduce LH levels through inhibiting leptin, nitric oxide, and gonadotropin-releasing hormone secretion (37).

In an investigation of the relationship between the use of metformin and its herbal substitute with body mass index, our findings showed a significant decrease in the average weight and BMI of patients during the study period in both groups; however, the BMI was significantly lower in metformin versus fenugreek group. On the other hand, the lipid profile of patients in both groups revealed significant improvement during the study. This improvement was significantly higher in fenugreek users than those consuming metformin. Therefore, in the former group, the average cholesterol, LDL, and TG level was lower and the average HDL level was significantly higher. This treatment also affected the levels of examined hormones including free testosterone, DHEAS, 17-hydroxyprogesterone, LH, and prolactin and demonstrated a significant reduction in all cases. In a study by Diamanti-Kandarakis et al., metformin treatment led to significant changes in sex hormone levels, which were consistent with our findings (38). Insulin resistance was another factor investigated in this research. The study revealed that the average insulin resistance decreased substantially in both groups after the treatment period. However, the improvements in insulin sensitivity were significantly greater in the fenugreek group compared to the magnitude of change in the metformin group. Similar to other research, our findings revealed that metformin improves insulin sensitivity and reduces insulin resistance markers in women with PCOS (2, 39).

At the cellular level, fenugreek seeds exert their hypolipidemic effects through intricate mechanisms. By influencing the expression of key genes like PPAR γ , PPAR α , and GLUT4 in insulin-responsive tissues, fenugreek seed extract helps stabilize plasma lipid levels in individuals with type 2 diabetes (40). This gene modulation plays a pivotal role in the beneficial effects of fenugreek by impacting lipid metabolism and insulin sensitivity at a cellular level. Moreover, in studies on obese rats fed a high-fat diet, fenugreek has demonstrated the ability to inhibit fat accumulation and improve dyslipidemia by intervening in processes

such as lipid digestion and absorption, glucose and lipid metabolism enhancement, insulin sensitivity improvement, antioxidant defense enhancement, and downregulation of lipogenic enzymes at the cellular level (12). These cellular mechanisms collectively contribute to the overall hypolipidemic properties of fenugreek seeds, highlighting their potential as a natural approach for managing lipid-related conditions.

A study by Swaroop et al. found that 94% of users benefited from the therapeutic effects of fenugreek seed extract. The study also revealed that a significant increase in the level of LH hormone which was associated with the use of fenugreek helped control the menstrual cycle and stimulate the growth of healthy eggs in the ovaries (41). In addition, no major harmful side effects of fenugreek were reported in included studies. It was noted that this herbal remedy caused a significant reduction in ovarian volume and the number of ovarian cysts including ALT, BUN and CK, highlighting its effectiveness in improving PCOS symptoms (41).

Metabolic disturbance, including insulin resistance, dyslipidemia, and hyperandrogenism play pivotal roles in PCOS-related infertility by impeding ovarian function, follicular development, and menstrual regularity (3). Fenugreek's capacity to enhance lipid metabolism and alleviate hyperandrogenism-linked symptoms, such as hair loss, suggests a potential indirect pathway to improving fertility outcomes by ameliorating metabolic obstacles to conception in PCOS patients. These findings propose adjunct therapies like fenugreek supplementation as potential complements to medication like metformin. Further exploration into the precise mechanisms underlying fenugreek's effects on metabolic and reproductive parameters in PCOS patients promises valuable insights into its role in optimizing fertility outcomes within this population.

Extensive endocrine assessment, comprehensive laboratory assessment, and investigation of weight changes, hirsutism, and menstrual disorders in patients were among the main strengths of the present study. Furthermore, to the best of our knowledge, this research was the first that investigated the effect of fenugreek on clinical signs and metabolic status of PCOS patients. The use of a triple-blind randomized clinical trial with parallel groups strengthened the study design and reliability of findings. The main limitation of the study was the short-term follow-up of patients, which

was attributed to logistical challenges. Future research should consider evaluating the long-term effects of fenugreek on infertility and ovulation in PCOS patients.

Conclusion

The results of this study showed that 60 days of supplementation with fenugreek at a dose of 333 gr per day can statistically improve glycemic status, lipid profile, and reduce hair loss (temporal baldness). Fenugreek cannot substitute metformin in PCOS-related hyperglycemia. However, given its lipid-lowering ability and low frequency of adverse effects, it can be used as an adjuvant treatment in PCOS, especially in PCOS patients with hyperlipidemia or moderate to severe hair loss.

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Conflicts of Interest

There is no conflict of interest.

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Supplementary table 1. Clinical features in two study groups before and after intervention

Variables	Metformin: Mean (SD) n=55	Fenugreek: Mean (SD) n=55	p-value
Weight (kg)			
Before intervention	76.1 (10.0)	76.8 (8.9)	0.67 *
After intervention	73.0 (9.8)	75.0 (8.9)	0.28 *
p-value	<0.001 #	<0.001 #	
BMI (kg/m²)			
Before intervention	27.6 (3.5)	27.9 (3.2)	0.68 *
After intervention	26.5 (3.5)	27.2 (3.3)	0.28 *
p-value	<0.001 #	<0.001 #	
WHR			
Before intervention	0.82 (0.0204)	0.83 (0.016)	0.307 *
After intervention	0.81 (0.0215)	0.82 (0.017)	0.307 *
p-value	<0.001 #	<0.001 #	
Hirsutism score			
Before intervention	11.1 (2.0)	10.6 (2.3)	0.25 *
After intervention	10.5 (2)	10.0 (2.2)	0.21 *
p-value	<0.001 #	<0.001 #	

* Compared between two study groups by independent t-test

Compared in each study group before and after the intervention by paired t-test

Supplementary table 2. Laboratory profile measures in two study groups before and after intervention

Variables	Metformin: Mean (SD)	Fenugreek: Mean (SD)	p-value
Lipid profile measures			
Cholesterol (mg/dL)			
Before intervention	182.9 (14.4)	181.7 (10.2)	0.5 *
After intervention	172 (14.5)	164.8 (10.2)	0.01 *
p-value	<0.001 #	<0.001#	
HDL (mg/dL)			
Before intervention	44.6 (8)	46 (7.5)	0.2 *
After intervention	47.3 (7.4)	52 (6)	<0.001 *
p-value	<0.001 #	<0.001#	
LDL (mg/dL)			
Before intervention	134.5 (17)	129.6 (11)	0.2 *
After intervention	121.4 (16.5)	114.3 (10.7)	0.04 *
p-value	<0.001 #	<0.001#	
TG (mg/dL)			
Before intervention	179.9 (15.5)	177.2 (16.8)	0.4 *
After intervention	165.9 (15.5)	158.3 (17)	0.01 *
p-value	<0.001 #	<0.001#	
Endocrine profile measures			
Testosterone (nmol/L)			
Before intervention	3.9 (1.6)	3.7 (1.5)	0.3 *
After intervention	3.8 (1.5)	3.6 (1.5)	0.5
p-value	<0.001 #	<0.001#	
DHEAS (μmol/L)			
Before intervention	3.6 (1.4)	3.4 (1.6)	0.7 *
After intervention	3.4 (1.4)	3.3 (1.5)	0.6 *
p-value	<0.001 #	<0.001#	
Hydroxyprogesterone (nmol/L)			
Before intervention	1.06 (0.3)	1.04 (0.31)	0.5 *
After intervention	0.9 (0.31)	0.87 (0.32)	0.6 *
p-value	<0.001 #	<0.001#	
LH (IU/mL)			
Before intervention	5.50 (2.86)	5.16 (2.67)	0.7 *
After intervention	5.41 (2.88)	5.02 (2.70)	0.6 *
p-value	<0.001 #	<0.001#	
TSH (mIU/ml)			
Before intervention	3.11 (1.41)	3.11 (1.52)	0.9 *
After intervention	3.14 (1.41)	3.18 (1.53)	0.8 *
p-value	0.203 #	0.003#	
Prolactin (425 μg/L)			
Before intervention	358.4 (146.7)	373.1 (166.1)	0.3 *
After intervention	347.6 (146.4)	353.8 (164.9)	0.5 *
p-value	<0.001 #	<0.001#	
FBS and insulin resistance measures			
FBS (mg/dL)			
Before intervention	91.9 (12.4)	90.8 (10.7)	0.5 *
After intervention	82.8 (10.9)	87 (10.4)	0.04 *
p-value	<0.001 #	<0.001#	

Contd. supplementary table 2. Laboratory profile measures in two study groups before and after intervention

Variables	Metformin: Mean (SD)	Fenugreek: Mean (SD)	p-value
Insulin resistance (HOMA-IR)			
Before intervention	1.6 (0.6)	1.5 (0.5)	0.4 *
After intervention	1.1 (0.5)	1.3 (0.5)	0.01 *
p-value	<0.001 #	<0.001#	

* Compared between two study groups by independent t-test

Compared in each study group before and after the intervention by paired t-test