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ASSESSING THE EFFECT OF PROCESSED *NIGELLA SATIVA* ON OLIGOMENORRHEA AND AMENORRHEA IN PATIENTS WITH POLYCYSTIC OVARIAN SYNDROME: A PILOT STUDY

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ABSTRACT: Objective: The aim of this pilot study was to assess the effect of processed *Nigella Sativa* (*N. Sativa*) on oligomenorrhea and amenorrhea in patients with Polycystic Ovarian Syndrome (PCOS). **Materials and Methods:** Ten women diagnosed with PCOS, having oligo-amenorrhea, participated in this study. The National Institutes of Health (NIH)'s criteria were used for the diagnosis. The patients, between 18 to 38 years old, were treated with 2 g/day of encapsulated processed *N. Sativa* for 16 weeks. This study compared menstruation habits before and after the medication. A series of metabolic and hormonal investigations was done at the beginning and the end of the study. Participants did not take any other medications. Monthly visits were done to assess the treatment. The effects of *N. Sativa* on the menstrual cycle was evaluated by four criteria: menstruation occurrence, menstruations intervals, menstruation severity and menstruation duration. The blood test results were analyzed using Stata version 13. **Results:** The average duration of menstruation and the ratio of cycle per month significantly increased during a 4-month intervention. In contrast, the average menstrual cycle intervals showed a remarkable decrease. 78% with mild menstruation before the intervention had moderate menstruation. Serum cholesterol, triglycerides, FBS, insulin, AST, LH and HOMA-IR index were significantly improved after the intervention. **Conclusion:** This study suggests that treatment with *N. Sativa* can be considered as a selective treatment in PCOS patients with oligo-amenorrhea, which needs more studies with bigger sample size and control group.

INTRODUCTION: Polycystic ovary syndrome (PCOS) is considered as one of the most common endocrinopathies among reproductive-aged women in the absence of other endocrine disorders such as thyroid dysfunction, congenital adrenal hyperplasia, Cushing syndrome, hyperprolactinemia, and androgen-secreting tumors, which affects 5-10% of the population [1]. PCOS can significantly impact women's quality of life as they express a constellation of symptoms includes menstrual dysfunction and androgen excess. Their health is threatened with the increased risk of multiple morbidities, including obesity, insulin resistance, diabetes mellitus type II (DM), cardiovascular disease (CVD), psychological

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disorders, infertility and even cancer [2]. PCOS is diagnosed with both following criteria of NIH 1990: (1) Menstrual irregularity; (2) Hyper-androgenism (clinical and/or biochemical) [1, 2].

Women suffering from PCOS often refer to Health care centers in order to manage their menstrual-related disorders, androgen-related symptoms, metabolic syndrome and infertility[3]. Appropriate management and lifelong follow-up is necessary for these patients so that complications could be detected and prevented as soon as possible. The most common pharmacological agents used for treatment of PCOS include insulin sensitizers, Oral Contraceptive Pills (OCP) and anti-androgenic agents. But these agents have some side effects. Thus, we need safer treatments with lower risks that will not have long- term side effects on patient [4].

According to documents and statistics revealed by World Health Organization, a new trend and popular interest and a significant move towards complementary medicine and especially traditional medicine can be seen in today's world. Many patients prefer to use more natural and the safest ways to cure their diseases [5, 6]. PCOS has not been referred as a certain disease in Iranian Traditional Medicine (ITM) or Persian medicine. One of the main symptoms of PCOS is amenorrhea and oligomenorrhea that is equivalent as "Ehtebas- e Tams" in ITM. Avicenna (980-1037 A.D), one of the most significant and globally known people both in Iran and around the world, has introduced several ways for treatment of oligo-amenorrhea in his most important book "The Canon of Medicine". Many herbs, either single or complex, have been used for treating this disease. *Nigella Sativa* (black-cumin) is one of them that have been referred as "Shoniz" in ITM. In addition to Avicenna's "The Canon of Medicine", this herb has been described in many traditional medicine manuscripts as an effective treatment for "Ehtebas- e Tams" that of course is just one of its numerous benefits [7, 8, 9].

N. sativa (Ranunculaceae) is an herbaceous annual flowering plant that grows better in dry and warm climate, from the perspective of ITM, *N. sativa* has a warm and dry nature with several functions but its traditional applications for women includes galactopoietics, emmenagogue" Moder-e Tams" [10].

Several benefits of this herb mentioned in different clinical studies include decreasing blood pressure, hypoglycemic and hypolipidemic effects, reducing aging process, antiatherogenic, antioxidant, anti-inflammatory, anti-acid and anti-seizure, anti-cancer, pain killer, protective effects on nerves, liver, kidneys and stomach, improving erectile dysfunction and menopause [11]. Although there are many studies about the effects of *N. sativa* on different diseases, no study yet has been conducted about its effects on oligo-amenorrhea, and other parameters of PCOS. Therefore, we aimed to investigate the effects of processed *Nigella sativa* on PCOS with oligo-amenorrhea.

DESIGN AND PROCEDURE:

Project Participants: This pilot study was conducted on a before-after basis on 10 patients with PCOS aged between 18-38 with diagnostic symptoms of oligomenorrhea or amenorrhea. They had been diagnosed according to NIH criteria and other primary investigation such as TSH, PRL, 17-OH progesterone and DHEA-S. The inclusion criteria included the desire and satisfaction of patient to be part of study, not taking hormonal medications and metformin in the past 3 months. Exclusion criteria were taking medications such as; hormonal medication anti-hypertensive, anti-hyperlipidemic, anti-diabetes, aspirin and other anticoagulant, anti-prostaglandins and unprescribed herbal medication, history of uncontrolled blood pressure, heart attack, cardiovascular diseases, stroke, cancer, liver, kidney and thyroidal disorders, DM Type l and ll, pregnancy, lactating and smoking. Patients with possible side effects, those who needed other interventions and surgery and also those who personally wanted to leave the study were excluded.

Method of Drug Preparation: A commercially available *N. sativa* was used in this study. *N. sativa*'s seeds were soaked in grape vinegar for at least 24 h, before they were dried and grounded to produce *N. sativa* powder. Capsules, containing 500 mg of *N. sativa*, were then made and prescription bottles of 60 capsules were prepared [7,10].

Study Design: Ethics Committee of Shahid Beheshti University of Medical Science with Ethics code of IR.SBMU.RETECH.REC.2017.838 (11th of January 2017) approved the study protocol.

The site of the study was Department of Traditional Medicine of Shahid Beheshti University. The aim of the study and its process were explained to the patients, after informed consent examiner completed medical history and menstrual questionnaire and blood test was performed including; AST, ALT, FBS, TG, Cho, HDL, LDL, LH, FSH, BUN, Cr, free testosterone and fasting insulin. The blood work was done in early follicular phase after a spontaneous or induced menstruation. Each patient received 2 capsules fasting and 2 capsules for night before bed. The results of the study were analyzed after 3 cycles of periods of consumption.

If no menstruation had occurred within one period (1 month), the capsule consumption was stopped for 1 week. Then, after one week wash out the second period of medication was started after ensuring from non-pregnancy. The third period was the same and all primary investigations were repeated at the end of this period (follicular phase).

At the end of each period of medication consumption, the patients were visited. Medication side effects questionnaire was completed, and next period medication was given to the patients. A phone contact with therapist was always available in the whole period of study. In order to evaluate the effect of *N. sativa* on oligo-amenorrhea, four criteria were used including; the occurrence of menstruation or the number of menstrual cyclicity during the intervention (the ratio of cycle per month), changes in menstrual cycle interval, duration and severity of bleeding. The severity of bleeding was evaluated with the Pictorial Blood-loss Assessment Chart (PBAC) [12] and also the duration by counting the number of menstruating days.

Statistical Analysis: Data were described as frequency (percent) for categorical variables and median (interquartile range) for continues variables. Wilcoxon signed ranked test was used to compare values before and after the intervention. $p<0.05$ was considered significant. All data analyses were performed using Stata version [13].

RESULTS: Of the 12 women participated in the study, 2 women were excluded from the project since they wanted to become pregnant as soon as possible. The mean age of women was 24.4 (SD = 4.1, min: 19, max: 30) and all of them were not sexually active. The mean age at menarche was 13.4 years old (SD = 1.11) and the mean duration of disease was 7.5 years (SD = 3.8). The average body mass index (BMI) were 26.2 (SD = 1.1). Half of women suffered from amenorrhea while the other half had oligomenorrhea. **Table 1** shows laboratory findings of patients before and after a 4-month trial. The level of serum cholesterol, triglyceride, FBS, insulin, AST, LH, and HOMA-IR index were significantly decreased after intervention.

TABLE 1: THE BLOOD TEST RESULTS OF THE PATIENTS WITH OLIGO-AMENORRHEA BEFORE AND AFTER A 4-MONTH INTERVENTION

Investigation	Before	After	P-value*
LH (IU/L)	10(7.3-16.7)	8.8(6.5-13)	0.007
FSH (IU/L)	8.6(6.9-9.7)	7.6(6.8-8.2)	0.28
Free testosterone (ng/dl)	2(0.9-2.7)	1.9(0.8-2.8)	0.28
BUN (mg/dl)	13(12-14)	13(11-15)	0.72
Creatinine (mg/dl)	0.7(0.6-0.8)	0.7(0.6-0.9)	0.6
AST (U/L)	25(18-35)	20(17-26)	0.03
ALT (U/L)	24(13-37)	23.5(15-30)	0.26
FBS (mg/dl)	96(92-99)	92(85-100)	0.05
Insulin (mlU/L)	11.8(10-14)	7(6.6-9)	0.005
HOMA	2.8(2.3-3.3)	1.8(1.4-2)	0.002
Quicki	0.32(0.31-0.32)	0.25(0.24-0.36)	0.26
Triglyceride (mg/dl)	96(66-150)	92(53-135)	0.04
Total Cholesterol (mg/dl)	184(165-219)	174(150-201)	0.04

Values are median (interquartile range). (BUN: Blood urea nitrogen; AST: Aspartate aminotransferase; ALT: Alanin aminotransferase; LH: luteinizing hormone; FSH: Follicular stimulating Hormone; HOMA: homeostasis model of insulin resistance; Quicki: quantitative insulin sensitivity check index; P-values are based on Wilcoxon-signed rank test).

The median duration of menstrual cycle significantly increased from 3 days (IQR: 2-5) to 5.5 days (IQR: 4-7) during 4- months of intervention, (**Fig. 1**, P-value= 0.02). Similarly, the

ratio of cycle per month (frequency of menstruation) significantly increased from 0.3 (IQR: 0.2-0.5) to 0.5 (IQR: 0.25-0.75). In contrast, the median interval of menstrual cycle showed a significant decrease from 90 to 45 days (**Fig. 2**, P-value=0.005).

After four months of intervention, the menstruation of seven patients (that is, 70% of participants) changed from mild to moderate (Mc Nemar P-value = 0.01).

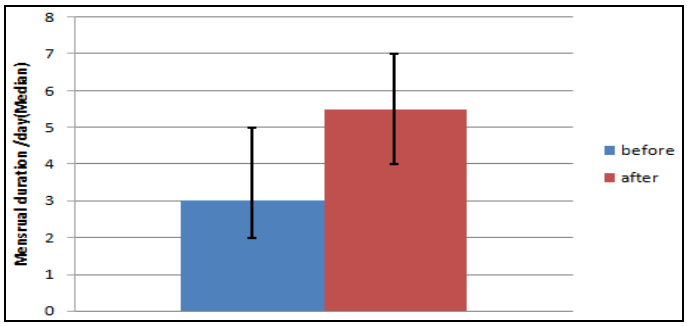

FIG. 1: CHANGE IN DURATION OF MENSTRUATION BEFORE AND AFTER THE INTERVENTION (the error bar indicated interquartile range) Wilcoxon-signed rank p-value= 0.02

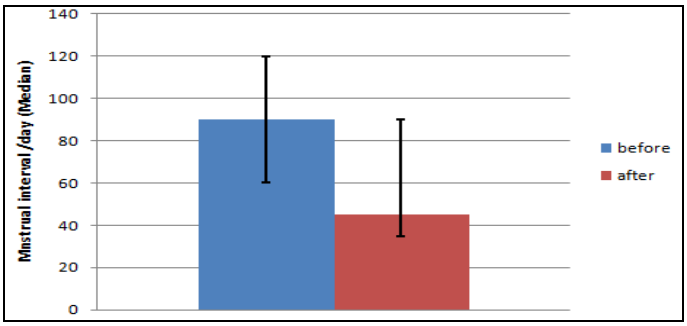

FIG. 2: CHANGE IN INTERVAL BETWEEN MENSTRUATION BEFORE AND AFTER THE INTERVENTION (the error bar indicated interquartile range) Wilcoxon-signed rank p-value=0.005

DISCUSSION: The aim of this study was to investigate the effect of *Nigella sativa* on oligo-amenorrhea in PCOS patients to induce ovulation as it often happens in regular cycles. As we know, oligo-anovulation leads to infertility. The results of this pilot study have shown that consumption of *N. sativa* can be effective in PCOS patients. In addition to induce bleeding and regulate menstruation, *N. sativa* could be effective on severity and duration of menstruation. Interestingly, our results have shown that the frequency of menstruation has been increased in all patients but in different ratios. Only 3 patients after intervention had one menstruation that belonged to amenorrhea group with one menstruation every 6 months. About interval, 4 patients (40%) had a menstruation with the first period of taking *N. sativa* (after one month), 3 of them had a menstruation after 1.5 to 2 months and 3 other patients had a menstruation after 3 period of treatment. It should be noted that the last group was from amenorrhea group with a 6-month menstruation cycle. Therefore, menstruation cycle intervals totally reduced which was a favourable result. Duration of bleeding increased in all patients except two cases. With regards to menstruation severity, in all but 3 patients (without any change in bleeding severity) mild bleeding severity turned to moderate severity.

Therefore, considering significant changes in oligo-amenorrhea indexes, *N. sativa* can have favourable effects on this symptom in PCOS patients.

Despite the widespread use of *N. sativa* in various issues, there are a few studies on the effects of *N. sativa* on women related issues. Latiff *et al.*, conducted a study on the effect of *N. sativa* on menopausal symptoms. The effect of *N. sativa* on the risk factors of metabolic syndrome were investigated in women near menopause and they found that *N. sativa* improves the quality of life, body mass index, total cholesterol, HDL, systolic and diastolic blood pressure. However, they pointed that more clinical and experimental studies are needed for ensuring these effects [13].

In an animal study conducted by Parhizkar *et al.*, the effect of methanol and hexane extract of *N. sativa* was investigated in improvement of vaginal epithelial cells in menopause mice. The results showed that *N. sativa* and especially its methanol extract have estrogenic effects that of course are lower than conjugated estrogens. This property can be used in the treatment of hormone replacement therapy in menopause stage; however, it still needs more investigation [14]. These studies suggest that *N. sativa* has phytoestrogenic effect, perhaps in our study; it is one of the effective mechanisms against oligo-amenorrhea.

Another positive effect of *N. sativa* in this study was the significant decrease in metabolic factors including triglyceride, cholesterol, AST especially FBS and fasting insulin, which led to improve insulin resistance.

Two HOMA-IR (fasting glucose (mmol/L) × fasting insulin (MIU/mL)/22.5) and Quicki ([log fasting glucose (mg/dL) + log fasting insulin (MIU/mL)] -1) indexes were used for measuring insulin resistance that both indexes improved in our study, but only changes of HOMA-IR was significant (P value= 0.0002). Although insulin resistance and other metabolic disturbances are not diagnostic criteria for PCOS, but it is observed in a large percentage of these patients, especially obese patients [15]. Positive effects of *N. sativa* on insulin resistance and other metabolic factors can also indirectly affect menstruation [16]. The metabolic effects of *N. sativa*, particularly its effect on diabetes has been shown in several studies [17].

Mohtashami *et al*., conducted a study on 70 healthy volunteers with normal lipid level and their results showed that receiving 2.5 ml *N. sativa* oil twice a day lead to decrease in total cholesterol level, LDL, triglyceride, fasting blood glucose and glycozilated hemoglobin. The result of our study was almost similar to the result of Mohtashami's study [18]. Sabzghabaei *et al*., conducted a study to evaluate clinical effects of *N. sativa* used for treating hyperlipidemia. Patients were divided into two groups that one group received *N. sativa* capsules consists of 500 ± 10 mg gronded *N. sativa* while the other group received placebo. A significant decrease was observed in the overall cholesterol, LDL, and triglyceride levels. *N. sativa* did not have any influence on fasting blood sugar and HDL. Its effect on FBS was contrary to our study.

Researchers suggested that more investigation on larger sample population should be conducted [19]. Also, Tasawar *et al*., in Multan, Pakistan [20] and Kateb *et al*., in Saudi Arabia [21] conducted a study on lipid profile and the effect of *N. sativa* on lipid profile in DM type II patients. Although our results were consistent with aforementioned studies, clinical studies on more patients, long period and control groups can strengthen our results. Therefore, we can use *N. sativa* products to control symptoms in PCOS patients as it is considered as a safer and healthier replacement for chemical medication.

Moreover, there are several studies about other medical herbs species on oligo-amenorrhea in PCOS patients. The study of lobo RA and Kort DH, prospective randomized double-blind study, showed that menstruation cycle improved in patients who received Cinnamon while no improvement was seen in placebo cases. The mechanism of influence on oligo-amenorrhea was not identified. Even, the suspected mechanism, improvement in insulin sensitivity, was not appreciated [22]. Of course, in common with our study, both studies showed a positive effect of both plants on the menstrual occurrence that possibly have had a similar mechanism such as effect on glucose metabolism and decrease body mass index (BMI) that in our study was not surveyed.

Another study was the effect of *Mentha longifolia* product on amenorrhea conducted by Mokaberinejad *et al*., The results of their study showed, at least one menstruation was observed in 73.7% of *Mentha longifolia* group compared to 30% in placebo group, regulated menstruation was observed in 33.3% of *Mentha longifolia* syrup group compared to 3.3% in placebo group for all three subsequent cycles and LH level had significant reduction in *Mentha longifolia* group [23]. In our study similarly, LH level has significant reduction. In the study of Mohebi *et al*., the effects of Fennel and OCP Low Dose (LD) were compared with regards to their effects on menstruation in amenorrhea caused by DMPA (Depot Medroxy Progestrone Acetate). Menstruation occurred in 73% of Fennel group and 81% of LD group compared to placebo group and average bleeding intensity was higher in Fennel group compared to LD group [24].

In a pilot study by Yavari *et al*., the effect of *Sesame* was investigated in 21 oligo-amenorrhea PCOS patients population whom 85% of them had a menstruation after using sesame. This study has been proved that *Sesame* can have phytoestrogeic effects [25]. In recent two studies, the both plants had phytostrgenic effect that was similar to our suspected mechanism. ITM philosophers, especially Avicenna believed that herbal medications work by different mechanisms. One of the mechanisms is dissolution (Tahlil).

Since, *N. sativa* has warm and dry quality. Therefore, it is very strong dissolvent (Mohalel). It solves waste moisture and decrease fat and compactness around waist and hip. Ultimately it

improves ovarian function and menstruation [7]. Our study limitations were primarily due to time limitation for primary blood test in follicular phase that made it difficult for patients to participate in study.

Moreover, since most of the patients are married and suffer from infertility they look for quicker treatment and do not accept to participate in this study which lead to a small size of study. In our study, no serious side effects were observed except one case of hoarseness occurrence that was resolved with simple commands.

CONCLUSION: This study suggests that treatment with *N. sativa* can be considered as an alternative treatment in PCOS patients with oligo-amenorrhea with no side effect. It of course needs more studies with bigger sample size and control group.

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CONFLICT OF INTEREST: None declared.

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