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Effectiveness of Aqueous Extract of Fenugreek Seeds and Flaxseed on Polycystic Ovarian Syndrome in Female Rats

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ABSTRACT

Polycystic ovarian syndrome (PCOS) is a disease impacting adult female in which its main features are hyperandrogenism, insulin resistance (IR), hyperinsulinemia, which enhances the probability of getting type 2 diabetes and cardiovascular disease. This study aimed to estimate the antidiabetic effect of fenugreek and the anti-androgenic effect of flaxseed and use the combination of both to treat polycystic ovarian syndrome in female rats. Forty Wistar rats were divided into five groups each contained eight rats, Group I: normal control, the rats in Group II-V received Estradiol valerate (4mg/kg in 0.4ml Sesame oil i.p.). Then, Group II served as PCOS control. The rats in Group-III were given fenugreek aqueous extract (100 mg/kg), Group IV received flaxseed aqueous extract (300 ml/kg) and Group V administered a combination of both extracts, for 60 consecutive days after PCOS conformation, extracts were given orally. The results showed that the Estradiol Valerate induced a dignified increase in glucose, insulin, insulin resistance, lipid profile, aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyltranspeptidase (GGT), and body weight in comparison to control. Moreover, an outstanding rise in serum LH, FSH, testosterone and a decrease in progesterone level, with no change in estradiol was detected. Furthermore, a significant rise in lipid peroxidation accompanied by an insignificant increase in nitric oxide, a significant decline in superoxide dismutase, catalase, and glutathione reductase activities in ovarian homogenates were also noted. Supplementation of fenugreek and flaxseed significantly attenuated these parameters. The results showed the beneficial effect of fenugreek and flaxseed in improving the impairment of IR and hyperandrogenism with corresponding disrupted parameters in polycystic ovarian syndrome.

Key words: *Hyperandrogenism, hyperinsulinemia, Insulin Resistance, Estradiol Valerate.*

INTRODUCTION

Polycystic ovarian syndrome (PCOS) form the greatest endocrinal disorders that influence women after reaching their procreation period age, [1] affecting around one of fifteen women widespread, distinguished by raised insulin and androgen levels, [2] which at latest leads to acne and hirsutism. It is also associated with insulin resistance (IR), obesity,[3] anovulation, and infertility on the prolonged incidence of cysts[4]. PCOS has been shown to be related to metabolic syndrome and its abnormalities [5, 6]. The major used diagnosis criteria of PCOS is Rotterdam criteria [7]. Clinical diagnostic criteria of PCOS is suggested to be the presence of hirsutism, hyperandrogenism, irregular menses, [8] metabolic syndrome characteristics, anovulation, and the polycystic ovaries [9]. PCOS etiology is not well recognized yet and trial animal models may assist to understand the pathophysiology of PCOS [10]. PCOS is correlated with hyperlipidemia and glucose intolerance in having a risk factor of type 2 diabetes, hypertension, cardiovascular disorder, and cancer [11]. Pharmaceutical medicines used for decades to treat PCOS include insulin sensitizers such as metformin and pioglitazone for hyperinsulinemia and hyperandrogenism, [12] oral contraceptives for hirsutism and menstrual irregularities, Spironolactone and finasteride for increased androgen, and clomiphene for infertility [13]. Complementary and alternative medicine

(CAM) is globally improving and preferred by individuals [14, 15]. There is demanding use of CAM therapies in an alternative to drugs for chronic diseases [16]. Fenugreek "(*Trigonellafoenum-graecum L.*)" is a leguminous, annual herb growing in India and North Africa [17]. It showed an anticancer effect against human hepatoma, [18] antidiabetic properties, [19] hypocholesterolemic effect, [20] and anti-inflammatory activity against arthritis in rats [21]. Flaxseed or linseed (*Linumusitatissimum L.*), it belongs to Linaceae family [22]. Flaxseed is loaded with bioactive components, which are efficient in the protection of some long-term illnesses like numerous types of cancer, cardiovascular diseases and cerebrovascular stroke, [23] and diabetes [24]. It is also rich in lignans, which showed to decline the level of androgen in males with prostate cancer [25]. This study was planned to assess the antidiabetic effect of fenugreek, the antiandrogenic effect of the flaxseed, and the effect of their combination in the treatment of polycystic ovary syndrome in female rats.

MATERIALS AND METHODS:

Experimental Animals

In this experiment, 40 female Wistar rats with the weight range between 170-200g were obtained from the Animal House of King Fahd Research Center, Jeddah, Saudi Arabia. The rats were kept at normal temperature and standard light cycle for one week before the experiment began to adapt with adequate food and water. The Animal Ethics Committee (Reference No 580-17) approved the experimental animal procedure in accordance with the guidelines for proper care and use of laboratory experimental animals of King Abdulaziz University.

Plant Material and Preparation

Fenugreek and flaxseed were purchased from a local traditional market in Jeddah, Saudi Arabia. 25 g of fenugreek seed was drenched in 100 ml of hot distilled water for 30 minutes, then filtered into a conical flask and the extract was collected and preserved for further usage [26]. 20 g of flaxseed [25] was soaked in 100 ml of hot distilled water and the same preparation of fenugreek was used.

Experimental Design

Rats were divided into five groups, each group with 8 rats. Group I was served as the normal control group and was given only distilled water. Group II-V were intramuscularly injected with 4 mg/rat (0.4 ml) of estradiol valerate dissolved in sesame oil once to generate the PCOS model. Vaginal smears were regularly taken and monitored under the microscope to ensure PCOS formation by watching the dominant cell type during their estrous cycle. Group II was served as the positive control PCOS-induced group and was given distilled water orally during the whole experiment period. Group III was addressed orally with 100 mg/kg of fenugreek aqueous extract daily. Group IV was daily given 300 mg/kg of flaxseed aqueous extract. Group V was daily administered with both 100mg/kg of fenugreek extract and 300 mg/kg of flaxseed extract. During the experiment, the body weight was recorded every week. After 60 days of treatment, blood samples were collected after euthanasia of rats with diethyl ether. Ovaries were removed and weighed. Serum was separated using a centrifuge and used for estimation of blood glucose, insulin, lipid profile : cholesterol and triglycerides levels, FSH, LH, estradiol, progesterone, and testosterone. IR was calculated by the homeostatic model assessment (HOMA) formula. AST, ALT, GGT were also estimated to study the liver function. Oxidative stress was as well studied in ovary tissues by estimating the activity of catalase, SOD, glutathione reductase, lipid peroxidation, and nitric oxide using a special kit purchased from Elabscience Company for each antioxidant.

Statistical Analysis

The data were analyzed using Megastat 10.0 add-in of Microsoft Excel program (2010). They were demonstrated as "mean ± standard deviation (SD)" by using One-way analysis of variance (ANOVA). Values higher than or equal to 0.05 were considered no significant difference and values less than 0.05 were counted as a significant difference.

RESULTS:

Vaginal Smear and Estrous Cycle

An irregular estrous cycle was spotted in EV-induced rats with respect to control with a predominance of cornified cells type indicating the constancy of the estrous cycle in most rats with PCOS (Fig 1).

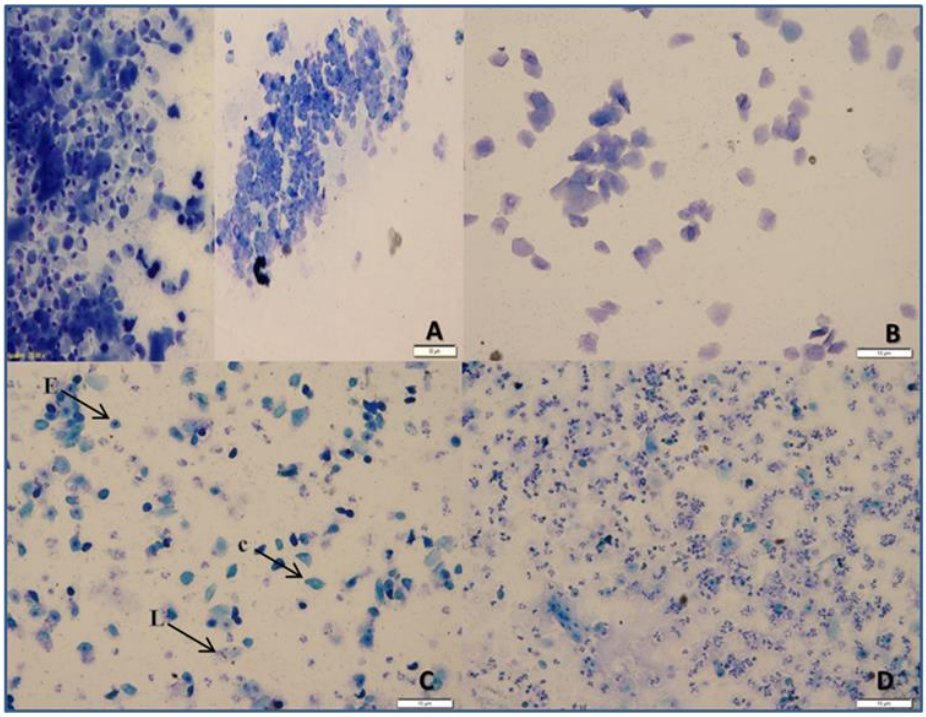

Figure 1: Vaginal smears of rats' estrous cycle showed different estrous phases with their presented type of cells (A) pro-estrous stage filled with E-epithelial cells, (B) estrous phase identified with c-cornified cells, (C) met-estrous phase with an equal amount of each cell type, and (D) diestrous stage mainly filled with L-leukocytes.

Body and Ovarian Weight

EV-induced rats revealed a significant increase in ovarian and body weight with respect to the control group with significant improvement after fenugreek and flaxseed supplementation (Fig 2).

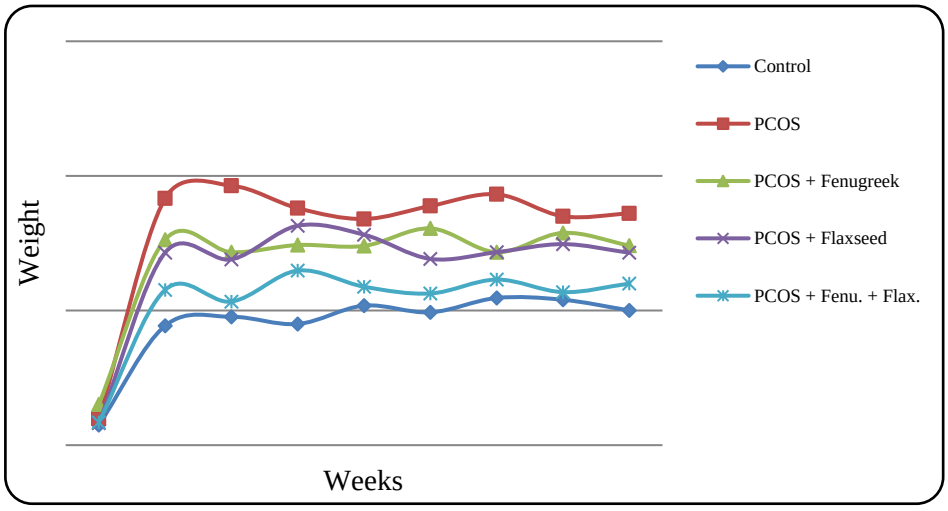

Figure 1: The Effect of EV and treatment of fenugreek and/or flaxseed on body weight of induced rats

Glucose, Insulin, and IR Status in Control, EV-induced and Treated Groups

Control group had normal levels of glucose, insulin, and IR while they were significantly higher in EV-induced rats. Administration of fenugreek and flaxseed showed a significant reduction in those parameters (Table 1).

Table 1: The effect of fenugreek and/or flaxseed on glucose, Insulin, and Insulin Resistance in EV- induced groups

Groups	Glucose (mg/dL)	Insulin (µU/ml)	HOMA - IR
Control	80.03 ± 9.10	6.30 ± 0.59	1.25 ± 0.17
PCOS	122.56 ± 4.58	21.57 ± 2.31	6.53 ± 0.87

	*** ^^^	*** ^^^	*** ^^^
PCOS + Fenugreek	106.63 ± 6.82 *** ### ^^^	13.63 ± 1.79 *** ### ^^^	3.59 ± 0.54 *** ### ^^^
PCOS + Flaxseed	112.50 ± 6.72 *** ### ^^^	18.06 ± 2.08 *** ### ^^^	5.03 ± 0.78 *** ### ^^^
PCOS + Fenugreek + Flaxseed	89.75 ± 8 ### **	9.27 ± 0.97 ### ***	2.04 ± 0.30 ### **

The values are the mean ± S.D. of parameters measured
$P < 0.01^{**}$, $P < 0.001^{***}$ significantly different from control group.
$P < 0.001^{###}$ significantly different from PCOS group.
$P < 0.001^{\wedge\wedge\wedge}$ significantly different from PCOS treated with Fenugreek + Flaxseed group.

Lipid Profile in EV- induced and Treated Groups:

Levels of cholesterol, TG, and LDL were significantly higher in PCOS group while HDL was reduced in comparison to control. These disturbed values were attenuated after supplementation of fenugreek and flaxseed (Fig 3).

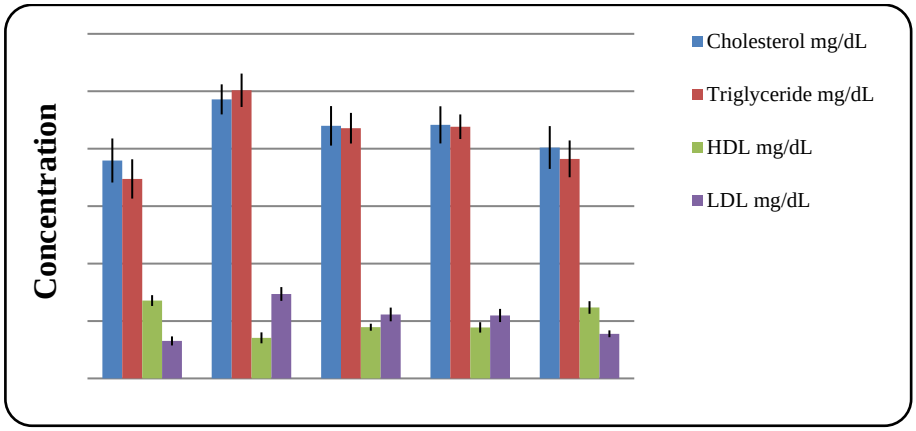

Figure 2: Effect of fenugreek and/or flaxseed on lipid profile parameters level in EV induced PCOS rat

Reproductive Hormones in EV-induced and Treated Rats

A significant increase was observed in LH, FSH, and testosterone after EV induction with a corresponding decrease in progesterone in contrast to control. On the other hand, estradiol was the same in all groups with no change. However, after administration of fenugreek and flaxseed, all FSH, LH, testosterone, and progesterone were significantly restored back to normal (Fig 4).

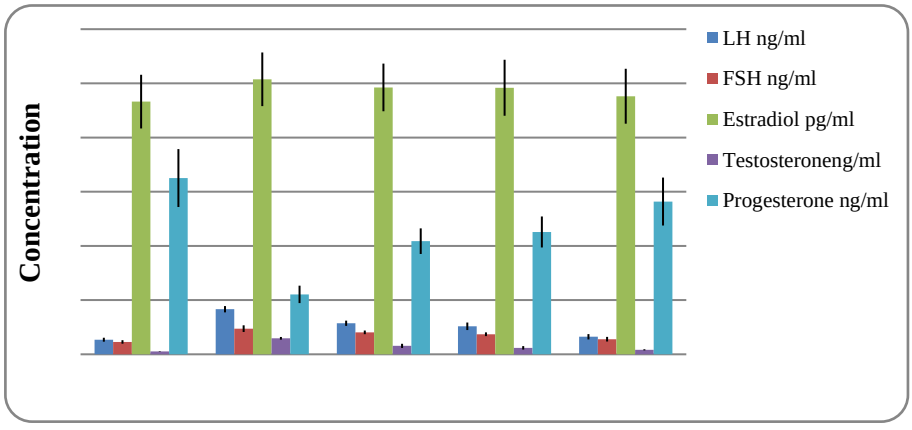

Figure 3: Effect of EV, fenugreek and/or flaxseed on the concentration of reproductive hormone parameters

Liver Enzymes in Control, PCOS, and Treated Groups

ALT, AST, and GGT showed a significant rise in EV-induced rats compared to those in the control, followed by a significant decrease in these liver enzymes after fenugreek and flaxseed supplementation (Fig 5)

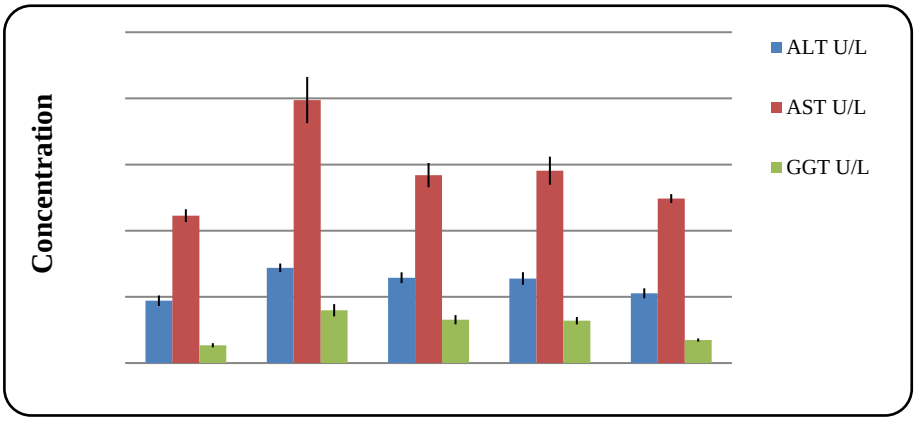

Figure 4: Effect of EV, fenugreek and/or flaxseed on liver enzymes

Oxidative Stress and Antioxidants in EV-induced and treated groups

Administration of EV to female rats provokes oxidative stress in ovaries, manifested by a significant concomitant increase in the levels of LPO, an insignificant increase in NO, a significant decrease in the activities of the antioxidants enzymes, SOD, CAT, and GR in ovarian tissues. On the other hand, in PCOS rats treated with fenugreek and/or flaxseed, a significant increase in the reduced antioxidants along with a significant decrease in LPO and NO was observed compared to the corresponding values in untreated PCOS rats (Fig 6 and 7).

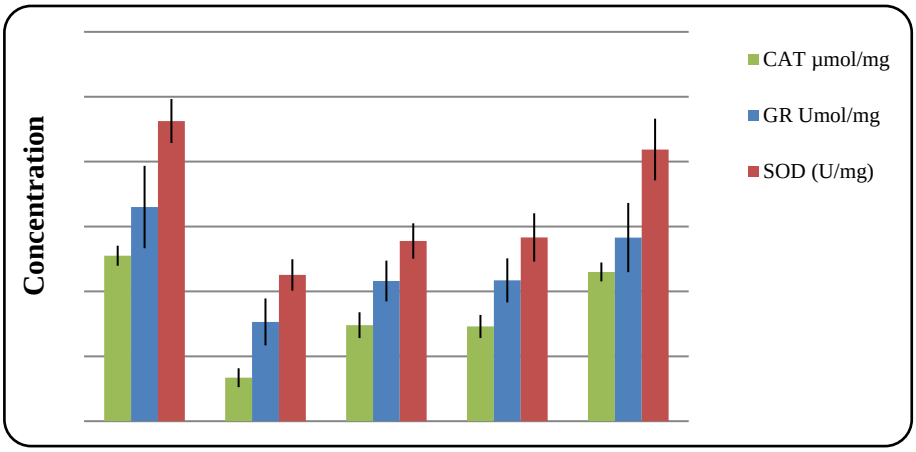

Figure 5: Effect of antioxidants in EV-induced and treated rats

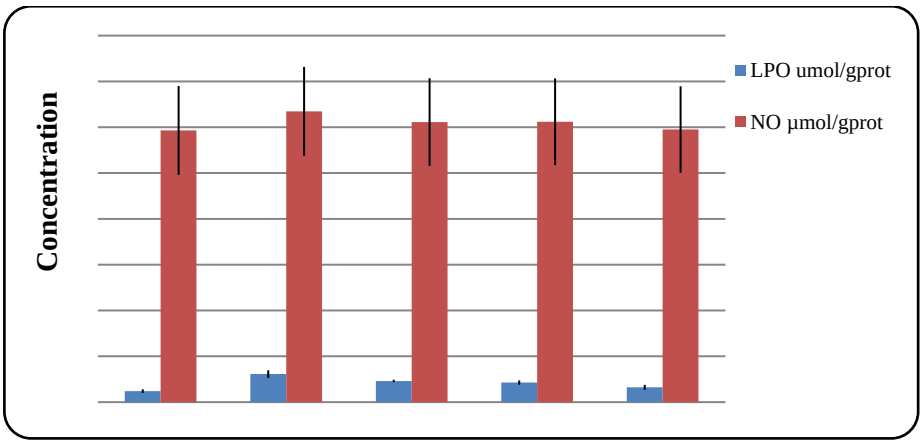

Figure 6: Effect of oxidants in EV-induced and treated rats

DISCUSSION:

The current study focused on the hypoglycemic effect of fenugreek and its influence on IR reduction, as well as the anti-androgenic effect of flaxseed concentrates in PCOS-induced rats in which the symptoms were the main treatment directions in this syndrome. The results showed a significant increase in body and ovarian weights of EV treated rats. Ghafurniyan *et al*. [27], Karimzadeh *et al.* [28], Jashni & Jahromi *et al*. [29], and Patel & Shah [12] concluded that the increase in ovaries and body weights attributed to the formation of cystic follicles in the ovaries of PCOS rats and increase in body fat. The treatment of PCOS rats with fenugreek and flaxseed showed improvement and a significant decrease in ovarian and body weights. Swaroop *et al*. [30] revealed a reduction in ovarian volume in PCOS subjects after administration of fenugreek seed extract, almost half of them showed reduced cyst size while 36% showed fully cyst degeneration. Muraki *et al*.[31]showed that fenugreek is effective against obesity and it decreases body fats. Moreover, Moradi *et al.* [32]pointed to the existence of fenugreek active components such as flavonoids, steroids, saponins, and alkaloids. These constituents have mainly antioxidant effect [33, 34].Moreover, these active contents probably participate in its effect on body and ovarian weight. Flaxseed treatment showed significantly reduced ovarian and body weights of PCOS rats. Farzana *et al*. [35] showed a dignified diminution in ovarian weight and follicles number after flaxseed administration in PCOS patients without any change in body weight while Pareek & Boolchandani [36] revealed a decrease in the mean of body mass index with no change in body weight. Cystic follicles number and thickness of the theca layer significantly decreased after flaxseed administration in EV-induced rats [37]. However, both plants containing compounds that benefit these two parameters by many means such as lignans, polyunsaturated fatty acids, alkaloids, steroids, flavonoids, and saponins [32-40].

EV induction caused a rise in blood glucose, insulin, and IR, which was consistent with Sasikala *et al*.[41], EV supplementation caused high androgen and IR leading to hyperinsulinemia. Several studies reported abnormal glucose metabolism associated with PCOS [42–44] and that might mainly be due to IR present in this syndrome. Fenugreek aqueous extract exhibited a considerable decline in serum glucose and insulin and improved IR, proving its hypoglycemic effect. This effect may be mediated by three ways, lowering glucose, decreasing cells sensitivity to insulin or by exhibiting insulin-like effects. Fibers in fenugreek play the main role in its hypoglycemic effect, active components and phytochemicals such galactomannan,[45] myecelin, flavonoids, saponins, glucosides, and pectin have shown antidiabetic effects that differ in the way of reducing glucose level [46]. Some components in fenugreek are also found in flaxseed including fiber and its glucose-lowering effect. There are different results about the effect of flaxseed on the glucose level. For example, Javidi *et al*. [47] observed no change in glucose and IR, when administered flaxseed powder daily to prediabetes patients, while Pan *et al*. [48] reported small but significant improvement in glycemic control in T2DM patients after lignan supplementation with no change in glucose and lipid profile or IR. In accordance with our study, Thakur *et al.* [49] observed a decrease in blood glucose after flaxseed gum supplementation in type II diabetic persons. Recently, Kapuriya *et al.* [24] announced that the flaxseed aqueous extract has antidiabetic activity in an experimental rat model. The current study showed that the combination of fenugreek and flaxseed possess the highest reduction effect on glucose among treatment groups.

In the current results, EV produced a significant rise in serum TC, TG, and LDL-c along with a significant drop in HDL-c. Knauff *et al*. [50] found that reduced insulin sensitivity involved in high TG concentration is associated with an increase in free androgens in PCOS. Since IR neglects insulin function in PCOS, hyperinsulinemia occurs; high lipid profile is expected in PCOS. In agreement with our results, Macut *et al*. [51], Lath [52], and Iuhas *et al*. [53] studies revealed that serum insulin, IR, TC, TG, and LDL-c levels were greater in PCOS compared to normal except HDL-c that was lower. Treatment of EV-induced rats with fenugreek and flaxseed aqueous extracts was notably diminished serum TC, TG, and LDL-c and raised HDL-c compared to untreated rats. Numerous studies showed that the same active components of fenugreek, which are involved in glucose reduction also participate in its lowering effect on lipids. Kassaian *et al*. [54] and Gupta & Verma [55] findings showed that administration of fenugreek to type II diabetic patients lowered TC, TG, VLDL-C, and LDL and lifted up HDL level, which might be due to the saponin and galactomannan of fenugreek that reduces its absorption from the intestine. lipid-lowering effect of fenugreek is owing to its suppression of fast assemblage and upregulation of low-density lipoprotein receptor [56]. Treating PCOS-induced rats with flaxseed showed a result similar to fenugreek and lipid profile was recovered. Thakur *et al*. [49] found a decrease in TC and LDL-c while Devarshi *et al*. [57] found a decrease in TG and VLDL-c with an increase in HDL in diabetic subjects after flaxseed supplementation. Torkan *et al*. [58] reported that flaxseed

administration to hyperlipidemic individuals reduced TC, LDL, and TG along with body weight and mass index. Kristensen *et al*. [59] showed that flaxseed dietary fibers decreased TC and LDL-c and increased fat excretion while Newairy & Abdou [60] revealed that reduced lipids were attributed to protective effects of lignan isolated from flaxseed. Abd El Ghany *et al*. [61] concluded that the lipid-lowering effect of flaxseed might be as a result of their rich content of polyphenols and flavonoids.

No change in estradiol but significant change in other measured reproductive hormones parameters was observed in PCOS rats; testosterone, FSH, and LH increased while progesterone decreased. In semi-agreement with our results, Pournaderi *et al*.[62] found a significantly high level of FSH, LH, and testosterone as well as E2 and progesterone in PCOS-induced subjects in contrast to control. Kakadia *et al*.[63] and Li *et al*.[64] as well found increased LH, FSH, and T while reduced E2 and progesterone in PCOS Letrozole-induced group. A study on Saudi PCOS women showed increased level of T and LH while FSH, progesterone and sex hormone-binding globulin (SHBG) levels decreased[65]. High insulin might be involved in high androgen. Botwood *et al*. [66] revealed that SHBG synthesis and secretion are inhibited by insulin. In this trend, Braga *et al*. [67] and Malini & Roy George [68] found that IR, insulin, T, and LHwere high in PCOS women while SHBG was lower. Novak*et al*. [69] proposed that PCOS anovulatory condition is due to high LH level caused by the abnormal passive feedback of E2 or progesterone on LH excretion. Because of various complications of PCOS and its unclear origin, it is difficult to point the exact mechanism involved in the syndrome. Fenugreek treatment showed a significant restoration in all of the measured sex hormones in EV-induced rats. Modaresi *et al*. [70] showed that fenugreek extract decreased FSH and LH and increased E2 along with folliculogenesis reduction in ovaries and concluded that fenugreek has infertility effect on healthy female mice. Swaroop *et al*. [30] showed that fenugreek reduced LH/FSH ratio and the number of ovarian cysts and also improved menstrual cycle in women with PCOS and some got pregnant. It is important to mention that fenugreek has a lipid-lowering effect and since E2 and androgen are mainly made of dehydroepiandrosterone (DHEA), which is made from cholesterol [71], it might help in androgen reduction. EV-induced rats treated with flaxseed revealed results similar to fenugreek so that T, FSH, and LH increased and progesterone decreased in them. As discussed, flaxseed enriched with lignans showed androgen reduction effect in PCOS women [72]. Jelodar *et al*. [37] observed an increase in progesterone level with a decrease in T after flaxseed extract supplementation to PCOS-induced rats, with no change in E2 and DHEA. Rietjens *et al*. [73] demonstrated that phytoestrogens have a structure similar to E2 enabling them to provoke anti-estrogenic effect by binding to estrogen receptors. Barnes *et al*. [74] as well mentioned that estrogenic or anti-estrogenic effect of phytoestrogen depends on the endogenous estrogen concentrations. Low fat intake might reduce androgen level, which might be due to flaxseed fibers and their decreasing effect on cholesterol. We think that reduction in androgen might be related first, to lipid reduction effect of flaxseed fibers, and second, to flaxseed lignans metabolites that may release anti-androgenic effect attributed to their negative feedback and reducing testosterone synthesis.

The liver has a vital executive role in various metabolic procedures, including lipid synthesis, transmission, and storage, as well as glucose and insulin metabolism that all related to PCOS [75]. Our result showed a significant increase in ALT, AST in PCOS group indicating the appearance of disrupted hepatic function in PCOS. Karoli *et al*. [76] and Gambarin–Gelwan *et al*. [77] detected similar results of increased liver enzymes in PCOS women, which is related to IR, obesity, dyslipidemia, and aging. Cree-Green *et al*. [78], Minato *et al*. [3], and Schwimmer *et al*. [79] findings showed an increase in AST and observed high IR, BMI, and dyslipidemia in PCOS subjects. In addition to high AST level, ALT and alkaline phosphate were high in EV-induced rats. Supplementation of fenugreek and/or flaxseed to EV-induced group manifested a notably reduced in the measured liver enzymes. El-Wakf *et al*. [80] observed a significant reduction in serum ALT and AST in nitrate-exposed rats after fenugreek administration.Moreover, Kaviarasan&Anuradha [81] used the polyphenolic extract of fenugreek seed to decrease liver damage and the increased liver enzymes in rats withchronicethanol administration, which were retrieved after extract administration. Kandhare *et al*. [82] confirmed the existence of anti-inflammatory, antioxidants, and anti-fibrotic activities in fenugreek extract given to induced-liver fibrosis rats with a decrease in AST, ALT, and GGT. This may be caused by phytochemicals in fenugreek. Yari *et al*. [83] showed the hepatoprotective effect of flaxseed against non-alcoholic fatty liver disease (NAFLD) in patients who administered it, causing reduced liver enzyme, IR, body weight, hepatic fibrosis, and fatty liver disease. Al-Bishri [84] said that flaxseed polyunsaturated fatty acids (PUFAs) comprising omega-3 and omega-6 fatty acids are responsible for the reduction of liver markers in hypertensive rats.

The ovarian of EV-induced rats showed oxidative stress (OS) sign, in which oxidants were higher than antioxidants. Birben *et al*. [85] implied that many disorders showed OS markers and reactive oxygen species

(ROS) produced from cellular metabolic activities and environmental factors. In PCOS, IR provokes OS production due to hyperglycemia and hyperlipidemia leading to ROS production [85,86]. Ghowsi *et al*. [86] evidenced that androgen is related to excess LPO and other OS markers in PCOS-induced rats. Papalou *et al*. [87] considered that PCOS is mainly an oxidative state where antioxidants unable to scavenge the excess free radicals. Some studies showed a significant decrease in SOD [88] and GSH while an increase in MDA and NO [89, 90] in PCOS subjects. Treating PCOS-induced rats with fenugreek and flaxseed have attenuated the imbalanced antioxidants to oxidants. Many studies showed the antioxidant effect of fenugreek against OS in PCOS and other disorders [91, 92]. Herrera *et al*. [93] and Baba *et al*. [94] detected a high amount of flavonoids and saponins in fenugreek extract. Subhashini &*et al*. [95], Dixit *et al*. [96], Mohammadzadeh *et al*. [97], Pandey & Awasthi [98] and Abeed Al Mashkor [99] showed that polyphenols and flavonoids are responsible for fenugreek antioxidant effect and scavenging free radicals in many disorders. Flaxseed also showed a protective effect against OS in PCOS and many other diseases [100–103]. Concerning flaxseed, various studies showed that lignans mainly secoisolariciresinol diglucoside (SDG) in flaxseed responsible in its antioxidant activity [60,104,105] as well as PUFAs such as omega-3 fatty acid [103] and rich phenolic compounds[104].

CONCLUSION:

The current study focused on the effect of fenugreek on insulin and IR and its hypoglycemic effect in PCOS-induced rats, as well as anti-androgenic effect of flaxseed. Both aqueous extracts of the two plants showed beneficial effect against serum glucose, insulin, IR, lipid profile, reproductive hormones, liver function, and OS. The combination of both fenugreek and flaxseed extracts showed better amelioration on all of these parameters and work synergistically to achieve the expected results.Therefore, current and future investigations will contribute to bridging the traditional knowledge of using natural products combination to reduce the symptoms of PCOS.

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