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A Comparison between the Effects of Evening Primrose Oil and Soybean Oil on Menopause Symptoms

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ABSTRACT

Background and Objective: More than 80% of women experience physical, vasomotor, sexual and psychological symptoms after menopause, and in 10-20% of women, the severity of menopause symptoms affects their quality of life. Due to the complications of using chemical drugs, this study was conducted to compare the effectiveness of evening primrose oil and soybean oil in postmenopausal women.

Methods: In this randomized controlled prospective study, 40 postmenopausal women were assigned into two groups of 20, 500 mg of evening primrose oil and 233 mg of soybean oil extract twice a day for 8 weeks. Measurement of serum hormones (follicle stimulating hormone, luteinizing hormone, estradiol), lipid profile, fasting blood glucose, and high sensitivity C-reactive protein were performed. Moreover, menopausal symptoms were analyzed and compared based on the evaluation score of menopausal symptoms (range 0-3).

Findings: The mean age of women was (51.65±3.7) years. After 2 months of treatment with evening primrose oil, there was a decrease in follicle stimulating hormone, luteinizing hormone levels concurred with increase in estradiol levels (-10.64%) (-8.09%) (7.47%), respectively ($p<0.05$). Meanwhile, women receiving the soybean oil revealed increase in all the three hormones (5.77%) (12.73%) (13.39%), respectively ($p<0.05$). Total cholesterol and triglycerides decreased in both study groups after treatment ($p<0.05$), fasting blood glucose level decreased in group 1 only (-1.39%), and high sensitivity C-reactive protein decreased in group 2 only (-22.33%) ($p<0.05$). In both groups, women presented with mild to moderate pre-treatment menopausal symptoms (Menopause Symptom Assessment score ranging from 0.75 to 2.25) showed significant decrease in their score up to no symptoms in each study group after 2 months (less than 0.75) ($p<0.01$).

Conclusion: The results of the study showed that both evening primrose oil and soybean oil supplements improve menopausal symptoms.

Keywords: *Postmenopausal Related Symptoms, Evening Primrose Oil, Soybean Oil, Menopause Symptom Assessment (MSA) Score, Biochemical Measures.*

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Introduction

Most women, but not all, experience embarrassing symptoms during pre- and/or post-menopause. The symptoms are either physical or psychological in nature (1). Up to 80% of women experience somatic, vasomotor, sexual, and psychological post-menopause symptoms, which are related to poorer self-rated health, decreased workplace productivity, and higher usage of public health insurance resources, substantially diminishing their overall life satisfaction (2). Post-menopausal symptoms such as night sweats, sweating, heart palpitations, and insomnia affect over 70% of women (3). Just about 10% to 20% of postmenopausal women have symptoms so severe that they significantly impact their quality of life, whereas the majority experience only mild discomfort. Menopausal symptoms might last for a long time (4).

Hormone treatment is the most effective treatment to achieve therapeutic alleviation of various menopausal symptoms, like vasomotor symptoms especially hot flashes (5), but many researchers advise keeping hormone replacement therapy to a minimum by using the smallest effective dosage for the shortest period possible (6). Many women use medicinal herbs as alternative therapies to get relief from menopausal-related symptoms especially the hot flashes (7). There are a number of non-hormonal treatments for menopause symptoms that have been described as helpful over-the-counter medications in medical research and the media (8). However, the benefits of these compounds have yet to be demonstrated with certainty, and these regimens are not completely free from side effects (9).

Evening primrose oil (EPO) is one of the most popular alternative treatments for women's health problems. This oil has been used for a long time to treat PMS, breast pain, menopause symptoms, and even to start labor (10). On the other hand, extracts of Soybeans are of particular interest in reducing menopausal symptoms especially hot flashes (11). Epidemiological studies have suggested that there is a link between countries that consume soy and decreased vasomotor symptoms (12). Effects of isoflavones constituent of soya bean used for hot flashes and co-occurring symptoms during the menopausal transition and early post menopause was previously investigated (13).

There was no clinical trial, up to our knowledge, to compare the effectiveness of EPO and soybean oil in Iraqi postmenopausal women with menopause-related symptoms. Evidently, there is a gap between the need for effective treatment and the treatment options available. Accordingly, this study was designed to compare their potential benefit in reducing the post-menopause-related symptoms like vasomotor symptoms (mainly hot flashes) and related metabolic and hormonal parameters.

Methods

This is a prospective comparative study conducted on 40 women who visit the private clinic and obstetrics-gynecology department in Fallujah Teaching Hospital; all were diagnosed with post-menopause-related symptoms; ages ranging from 45 to 59 years; were enrolled under the supervision of an obstetrician-gynecologist; all women completed the study and were treated according to the practice guidelines. The inclusion criteria included post-menopausal women presented with post-menopausal symptoms, as defined by the Stage of Reproductive Aging Workshop (STRAW) Working Groups (14) such as vasomotor (hot flashes, sweating), mental (insomnia, migraines, irritability), or physical (vaginal, genital) in nature (vaginal dryness, dyspareunia) symptoms. Exclusion criteria included postmenopausal women at high risk or survivors of breast cancer, on warfarin or other antithrombotic drugs, with history of neurological disorders and mental illness, used hormone replacement therapy, on sedatives or anti-anxiety drugs regularly. The ethics code was obtained from Institutional Scientific Ethics Committee (research number 21-code number

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9). The project was accepted by field authorities. The patient's oral and written consent was taken after a full explanation of the aim of the study and ensuring the reliability of the collected information.

The selected patients were randomly allocated (using simple randomization method) into two main groups; Group 1 included 20 postmenopausal women who received 500 mg EPO (40 mg gamma-linolenic acid), as 2 capsules twice a day for 8 weeks. Group 2 included 20 postmenopausal women who received 233 mg soybean oil extract (70 mg soy isoflavone), as 2 capsules twice a day for 8 weeks. The patients were informed to take the complement with or after meals, then followed up for any adverse effects until the end of the study.

The treatment outcome measures include the severity of postmenopausal symptoms through daily monitoring for frequency of vasomotor (mainly hot flashes (HFs) and night sweats (NSs)) symptoms, also the changes in biochemical indices. All measures were conducted at baseline and endpoint (after 8 weeks). Data were collected by the researcher; a special sheet was designed by the research team to match the study goals and the information was collected from the patient's case sheets regarding their demographic data, which included age, residence, Body Mass Index (BMI), menopause symptom and medical history, and were collected from women via face-to-face interviews with the researcher.

The hormones parameters, follicle stimulating hormone, luteinizing hormone, and estradiol (FSH, LH, & EST) were estimated based on Electrochemiluminescence (ECL) using Cobas diagnostic kit (Roche/Hitachi Cobas E411) with a fully automated immunoassay analyzer. The normal value of FSH, LH, EST at Menopause stage were (17.0-95.0) mIU/mL, (8.0-33.0) mIU/mL, and (<58.0) pg/mL, respectively (15). The lipid profile, total cholesterol, triglycerides, and high-density lipoprotein (TC, TG, & HDL) were estimated using Cobas diagnostic kit based on the enzyme-driven reaction, determined by a fully automated chemical analyzer. Low density lipoprotein (LDL) concentration was determined by traditional Fried Ewald's (16). Blood sugar was estimated based on the enzyme-driven reaction using Cobas diagnostic kit with a fully automated chemical analyzer. Diagnosis of women with diabetes is made when fasting blood glucose (FBG) levels are consistently over 200 mg/dL (17). The highly sensitive C-reactive protein (hs-CRP) was estimated using immunoturbidimetric assay, using Cobas diagnostic kit (Roche/Hitachi Cobas C311) with a fully automated chemical analyzer. Results for standard hs CRP test are usually given as follows: Normal (Negative): Less than 10 mg/L. High (Positive): Equal to or greater than 10 mg/L (18).

The Menopause Symptom Assessment scale consists of 44 items, representing 6 domains as sub-scales, that assess menopausal complaints. High scores show more menopausal complaints and reduced quality of life. The minimum score that participants can get from this scale is 0, and the maximum is 44. The MSA is a universally standard and validated 4-point Likert scale for the quantifiable resolve of the severity of the symptoms as follows: None [0-0.75), Mild [0.75-1.50), Moderate [1.50-2.25), and Severe [2.25-3] (19).

The data were analysed using Microsoft Excel 2021 and Statistical Package for Social Sciences (SPSS, IBM, version 26.0) software. The results reported in this study were expressed as mean±SD, and frequencies were expressed as percentages. For comparisons among distributed groups, an analysis of covariance (ANCOVA) and independent T-test were performed. The chi-squared test was used to compare reported proportions of subject satisfaction scores, and Likert Scaling was used for MSA score. Probability values (p-values) less than 0.05 were considered a biologically significant difference, while probability values less than 0.01 were regarded as highly significant.

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Results

Demographics and Disease Characteristics of Participants: In the current study, the mean age of women who received EPO was 52.4±4.1 years, while the mean age of women who received Soybean oil was 50.9±3.3 years. The mean BMI of women who received EPO was (33.15±5.3) Kg/m^2, and most of them were overweight (45%), while the mean BMI of women who received Soybean oil was (32.23±6.1) Kg/m^2, and most of them were obese class 1 (35%). Most women in both groups (1 and 2) did not have a history of chronic illness (70% and 65%, respectively), and any history of previously taking any medications (80% and 100%, respectively). The mean duration of menopausal symptoms of women in group 1 was (14.55±7.4) months, who were presented with less than 7 times hot flashes per day (60%). However, the mean duration of menopausal symptoms of women in group 2 was (11.95±4.5) months, who were presented with less than 7 times hot flashes per day (55%) (Table 1). Most socioeconomic factors did not reveal significant difference between the two study groups (p>0.05).

Table 1. Scio-Demographic characteristics of the study groups

Variables	Study Groups		Total (n=40)	Sig.
	G1 (n=20) Mean±SD or Number(%)	G2 (n=20) Mean±SD or Number(%)		
Age (years)	52.4±4.1	50.9±3.3	51.65±3.7	>0.05$^{N.S.}$
BMI (Kg/m^2)	33.15±5.3	32.23±6.1	32.69±5.7	>0.05$^{N.S.}$
Chronic Diseases				
With	6(30)	7(35)	13(32.5)	>0.05$^{N.S.}$
Without	14(70)	13(65)	27(67.5)	
Medication History				
No	16(80)	20(100)	36(90)	<0.05*
Yes	4(20)	0(0)	4(10)	
Menopausal Symptoms (months)	14.55±7.4	11.95±4.5	13.25±6.2	>0.05$^{N.S.}$
Number of Hot Flashes per day				
<7 times/day	12(60)	11(55)	32(57.5)	>0.05$^{N.S.}$
>7 times/day	8(40)	9(45)	17(42.5)	
Total	20(100)	20(100)	40(100)	

Chi-square were used for categorical variables, and independent T-test were used to compare between two means. N.S: Not significant (p>0.05), *Significant (p<0.05).

Effect of Evening Primrose Oil and Soybean Oil on Biochemical Measures: The FSH level significantly decreased in group 1 (55.94±5.5) mIU/mL with a percentage difference (-10.64%) compared to the estimated baseline (62.6) mIU/mL, while increased in group 2 (66.21±3.7) mIU/mL with a percentage difference (5.77%). The LH level decreased in group 1 (33.50±5.5) mIU/mL with a percentage difference (-8.09%) compared to the estimated baseline (36.45) mIU/mL, while increased in group 2 (41.09±3.2) mIU/mL with a percentage difference (12.73%). The EST level significantly increased in both groups, in group 1 (73.49±4.8) pg/mL with a percentage difference (7.47%) compared to the estimated baseline (67.43) pg/mL, and in group 2 (76.49±3.0) pg/mL with a percentage difference (13.39%). There were significant differences between the two study groups (p<0.05) in respect with hormonal levels (Table 2).

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The TC level decreased in group 1 (193.58±6.0) mg/dL with a percentage difference (-0.82%) compared to the estimated baseline (195.18) mg/Dl, and decreased in group 2 (191.66±4.2) mg/dL with a percentage difference (-1.8%). The TG level decreased in group 1 (159.52±10) mg/dL with a percentage difference (-14.34%) compared to the estimated baseline (186.22) mg/dL and slightly decreased in group 2 (186.59±7.2) mg/dL with a percentage difference (0.2%). The HDL level decreased in group 1 (43.22±2.4) mg/dL with a percentage difference (-6.33%) compared to the estimated baseline (46.14) mg/dL and increased in group 2 (46.69±1.5) mg/dL with a percentage difference (1.19%). The LDL level slightly decreased in group 1 (113.50±54.9) mg/dL with a percentage difference (1.86%) compared to the estimated baseline (111.43) mg/dL and increased in group 2 (175.49±40.9) mg/dL with a percentage difference (57.49%). Regarding lipids, except for HDL and LDL, there were statistically significant differences between the two study groups for TC and TG ($p<0.05$) (Table 2).

The FBS level decreased in group 1 (104.30±5.8) mg/dL with a percentage difference (-1.39%) mg/dL compared to the estimated baseline (105.77) mg/dL and increased in group 2 (107.94±4.4) mg/dL with a percentage difference (2.05%). Regarding FBS, there was a statistically significant difference between the two study groups ($p<0.01$). Finally, the hs-CRP level slightly increased in group 1 (4.45±0.7) mg/L with a percentage difference (3.49%) compared to the estimated baseline (4.3) mg/L and decreased in group 2 (3.34±0.5) mg/L with a percentage difference (-22.33%). Regarding hs-CRP, there was a statistically significant difference between the two study groups ($p<0.05$).

Table 2. Effect of the study interventions on Biochemical Measures after 2 months

Variables and Study Groups	E. Baseline	E. End Line Mean±SE	p-value	% Difference
FSH (mIU/mL)				
G1	62.6	55.94±5.5	$<0.01^{**}$	-10.64%
G2		66.21±3.7		5.77%
LH (mIU/mL)				
G1	36.45	33.50±5.5	$<0.05^{*}$	-8.09%
G2		41.09±3.2		12.73%
EST (pg/mL)				
G1	67.43	72.47±3.3	$<0.01^{*}$	7.47%
G2		76.46±2.9		13.39%
TC (mg/dL)				
G1	195.18	193.58±6.0	$<0.05^{*}$	-0.82%
G2		191.66±4.2		-1.80%
TG (mg/dL)				
G1	186.22	159.52±10.0	$<0.01^{**}$	-14.34%
G2		186.59±7.2		0.20%
HDL (mg/dL)				
G1	46.14	43.22±2.4	$>0.05^{N.S.}$	-6.33%
G2		46.69±1.5		1.19%
LDL (mg/dL)				
G1	111.43	113.50±54.9	$>0.05^{N.S.}$	1.86%
G2		175.49±40.9		57.49%
FBS (mg/dl)				
G1	105.77	104.30±5.8	$<0.01^{**}$	-1.39%
G2		107.94±4.4		2.05%
hs-CRP (mg/l)				
G1	4.3	4.45±0.7	$<0.05^{*}$	3.49%
G2		3.34±0.5		-22.33%

Analysis of Covariance was used. **Highly Significant ($p<0.01$). *Significant ($p<0.05$). %: percentage differencep.

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Effect of Evening Primrose Oil and Soybean Oil on Menopause Symptom Assessment: The current findings revealed statistically significant decreases in Menopause Symptom Assessment (MSA) score within each study groups after two months of treatment compared to pre-treatment ($p<0.01$). After two months of treatment, women in group 1 who received EPO showed a decrease in MSA score of (-60.8%) compared to the estimated baseline of (1.48) and a decrease in group 2 who received soybean oil of (-56.1%). In this study, after 2 months of treatment, EPO significantly decreased all menopause symptoms as follows: somatic (-58.2%), emotional (-57.0%), bladder (-58.0%), sexual (-62.5%), personality (-64.3%), and menstrual (-58.8%) disorders. Soybean oil also significantly reduced all menopausal symptoms, including somatic (-58.2%), emotional (-53.7%), bladder (-54.7%), sexual (-56.3%), personality (-59.2%), and menstrual (54.5%) disorders. In this study, after 2 months of treatment, EPO had significantly decreased all menopause symptoms more than soybean oil except personality and somatic domain ($p<0.01$) (Table 3). Using Pearson correlation coefficient, after two months of treatment, there was a significant strong linear negative relationship between MSA score and EST level in women who received EPO ($p<0.01$, $r>0.5$), whereas in women who received soybean, there was a significant moderate linear positive relationship between MSA and FSH level ($p<0.05$, $r=0.40$).

Table 3. Effect of the study interventions on Menopause Symptom Assessment (MSA) Questionnaire after 2 months

Variables and Study Groups	E. Baseline	E. Endline	p-value	% Difference
Somatic				
G1	1.53	0.64±0.04	<0.01**	-58.2%
G2		0.64±0.03		-58.2%
Emotional				
G1	1.49	0.64±0.04	<0.01**	-57.0%
G2		0.69±0.03		-53.7%
Bladder				
G1	1.50	0.63±0.05	<0.01**	-58.0%
G2		0.68±0.04		-54.7%
Sexual				
G1	1.44	0.54±0.05	<0.01**	-62.5%
G2		0.63±0.04		-56.3%
Personality				
G1	1.47	0.61±0.05	<0.01**	-58.5%
G2		0.60±0.04		-59.2%
Period				
G1	1.43	0.51±0.04	<0.01**	-64.3%
G2		0.65±0.03		-54.5%
Total Score of MSA				
G1	1.48	0.58±0.03	<0.01**	-60.8%
G2		0.65±0.02		-56.1%

Analysis of Covariance had used. **Highly significant ($p<0.01$). %: percentage difference.

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Discussion

The current findings revealed that 2 months supplement with 1000 mg of EPO produced improvement in post-menopausal sex hormones, i.e., decrease in FSH and LH levels concurred with increase in EST levels. When levels are naturally low at menopause (20), the gamma linoleic acid (GLA) found in the EPO has an estrogenic action, suggesting that it may act on estrogen receptors to increase endogenous estrogen levels (21). The direct effect of EPO on hormonal levels was not assessed in other previous studied up to the best search, hence no comparative findings available, nevertheless, the hormonal improvement after EPO supplement was reflected through its reducing severity of vasomotor symptoms of menopausal women as will be mentioned later.

On the other hand, Soybean did not impact FSH, LH, or EST levels, according to another previous study by Hooper et al., where a small, non-statistically significant rise in circulating estradiol was associated with higher consumption of soy meals and supplements (22). This finding was not in line with current study, since women who received a total of 466 mg soybean oil extract (70 mg soy isoflavone) for 2 months revealed increase in all the three sex hormones significantly. Inverse results were reported by Kim, et al. who found that after 12 weeks of taking a 70 mg/day isoflavone containing supplement, postmenopausal women's LH levels decreased significantly ($p=0.027$), while FSH, estrone, and estradiol levels remained unchanged (23). Also, Enjezab et al. found a decline in FSH, LH, and EST levels after 3 months, but they did not find a statistically significant decline in any of the hormones except estradiol (24).

Menopause is associated with negative changes to lipid profile (25). After 2 months of treatment, post menopause women who received EPO and soybean oil produced lower levels of TC. Though TG decreased after EPO regimen mostly in the current study, previous meta-analysis stated that EPO has a positive influence on lipids, including the decrease of TG and VLDL and the increase in HDL (26). Abdulridha et al. reported that a dose of 500 mg EPO twice a day for 8 weeks produced beneficial effect on lipid profile in type 2 diabetic patients (27). In a previous study, a dose of >80 mg/day of soybean oil significantly enhanced lipid profiles, and an effective dose of 15-30 g/d was reported for the decrease of TC, TG, and LDL-C (28), as in the current findings. Diastolic blood pressure and serum LDL were both reduced by soy protein, but HDL was unaffected (26). Menopausal women who ate isolated soy proteins had improvements in their HDL level (29).

After two months of treatment with EPO in this study, there was slight decrease in FBG levels by -1.39%. This findings are in line with previous report where supplementing EPO with vitamin D for six weeks improved glycemic control in women with gestational diabetes (30). Additionally, diabetic patients who received 4 grams of EPO daily for 4 weeks did not experience any improvement in glycemic control (31). On the other hand, the current results showed slight increase in FBG in women who received soybean by 2.05%. In a previous study, 6 months of 100 mg soy treatment produced reduction to 85% FBS level compared to baseline (32). The inverse findings of soya bean oil in the current study are probably due to shorter duration of treatment and its indirect effect on metabolic pathway.

In this study, women who received EPO showed significant increase in hs-CRP levels (3.49%) compared to significant decrease after soybean oil supplement by (-22.33%). A previous study reported anti-inflammatory and cardioprotective properties (33). Prostaglandins derived from GLA affect inflammatory responses in blood vessels, allowing for the management of vasomotor symptoms. Moreover, it was previously reported that soy isoflavones lower hs-CRP levels significantly in postmenopausal women who have high levels (34). Studies have revealed a favorable correlation between elevated levels of hs-CRP and both E2 and frailty (35, 36)

In the current study, in both study groups, women were presented with mild to moderate post-menopausal symptoms (MSA scores ranging from 0.75 to 2.25). However, after 2 months of both herbal supplements

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(EPO and Soybean Oil), significant improvements in the severity of post-menopausal symptoms were seen with a decreasing MSA score up to no symptoms (less than 0.75), where women who received EPO adapted more effectively in terms of symptoms than those who received soybean oil. In agreement with current findings, Yousefi et al. found that EPO can help reduce the amount and frequency of sweating that comes with menopause (37). Furthermore, Motaghi Dastenaie et al. indicated the significant effect of the evening primrose oil on reducing hot flashes in postmenopausal women compared to women taking the placebo (38). Moreover, the application of 8 weeks of oral EPO (500 mg twice a day) is effective in the reduction of the severity of hot flashes and improvement of the quality of life, but it seems that it is not effective in reducing the number of hot flashes (39). Current results were inconsistent with other recent studies (40, 41). Kazemi et al. (2021) reported that the use of 1,000 mg EPO twice a day effectively lowered the frequency and severity of night sweats after 8 weeks with statistically significant differences ($p<0.05$) compared to control group who received the same amount of placebo (40).

In contrast, Farzaneh et al. compared taking 500 mg of EPO orally for 6 weeks with a placebo as a treatment for hot flashes. EPO group experienced an increase in the frequency, severity, and duration of hot flashed, but only the severity of hot flashes was significantly better in this group compared with the control group, with increases in social and sexual activity as well as the quality of life (42). Also, Mehrpooya et al. stated that number of hot flashes in EPO group in the 8th week showed no significant difference in blocked randomization study ($p=0.32$) (41). Some conflicting findings on the drug's ability to alleviate hot flashes could be attributed to differences in dosage (40).

On the other hand, and in agreement with current findings, another study found that postmenopausal women taking soy supplements experienced just a mild improvement in their hot flashes (43). Another study reported that women receiving 100 mg of isoflavone extract daily for 4 months experienced significant reduction of menopausal symptoms (44). A daily dose of 45 mg or higher of soy is recommended to replace conventional hormone replacement therapy (45). Due to lack of research protocols including isoflavone component and dosage, outcomes, and trial duration, it is difficult to reach a conclusion. Nevertheless, the use of isoflavones is warranted due to their safety profile and benefit to overall health.

Both EPO and soya bean oil supplements improved postmenopausal symptoms and related sex hormones and biochemical measures, giving a promising alternative to hormone treatment.

Conflict of interest: Authors declare none.

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