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Evening Primrose (*Oenothera biennis*) 'A miracle gift of nature' for females

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Evening primrose oil (EPO) present in the Native to North and South America and now widespread throughout Europe and parts of Asia, extracted from *Oenothera biennis*, Known with different names tree primrose, sun cups, sun drops, king's cure-all, fever plant, evening star, and night willow-herb. EPO oil contains majorly non-essential ω -6 polyunsaturated fatty acid γ -linolenic acid (GLA~9%), the essential ω -6 polyunsaturated fatty acid linoleic acid (LA~75%), oleic acid, palmitic acid, and stearic acid. It has significant protective role in covering female issues such as premenstrual symptoms, breast pain (mastalgia) and menopausal along with cervical ripening, and labor induction or augmentation. Evening primrose is the precursor of eicosanoids, which has anti-inflammatory and anti arithrogenic properties. It seems that evening Primrose oil can be first line of treatment in females without any side effects. Therefore, further studies are required to improve our understanding of EPO action on female management.

Keywords: *Oenothera biennis*, evening primrose oil, mastalgia, menopause

INTRODUCTION

Natural herbs was used the alternative therapy before the development of synthetic remedies use as a medication to treat certain health associated problems (Kazemi et al. 2021; Montserrat-de la Paz and Garcia-Gimenez, 2014). Evening primrose oil (EPO) is extracted from the seeds of *Oenothera* L. occurs in America as well tropic regions, belongs to the family *Onagraceae* have been studied and known as the 2nd targets genus with 145 known species among which *Oenothera biennis* also known as evening primrose commonly is the most studied due to its significant biological actions majorly in female's ailments. The other names *Oenothera biennis* are sun cups, kings cure-all, sun drops, evening star, night willow herb and fever (Munir et al. 2017; Timoszuk et al. 2018). Methalonic extract obtained from the aerial part of the Evening

Primrose showed that it mainly contains Flavonoids and Phenolic acids. Phenolic acids 3-p-feruloylquinic acid, 3-p-coumaroylquinic acid, 4-p-feruloylquinic acid, caffeic acid, pentoside, valoneic acid, dilactone, gallic acid with its ester derivatives (methyl gallate, galloylglucose, digalloylglucose, and tris-galloylglucose) and ellagic acid with its ester derivatives (ellagic acid hexoside and ellagic acid pentoside) (Granica et al. 2013). Flavonoids in *Oenothera biennis* are myricetin 3-O-glucuronide, quercetin 3-O-galactoside, quercetin 3-O-glucuronide, quercetin 3-O-glucoside, quercetin pentoside, quercetin dihexoside, quercetin glucuronylhexoside, quercetin 3-O-(2'-galloyl)-glucuronide, kaempferol 3-O-rhamnoglucoside, kaempferol 3-O-glucoside, kaempferol 3-O-glucuronide, kaempferol 3-O-(2'-galloyl)-glucuronide, and kaempferol pentoside (Johnson et al. 2019).

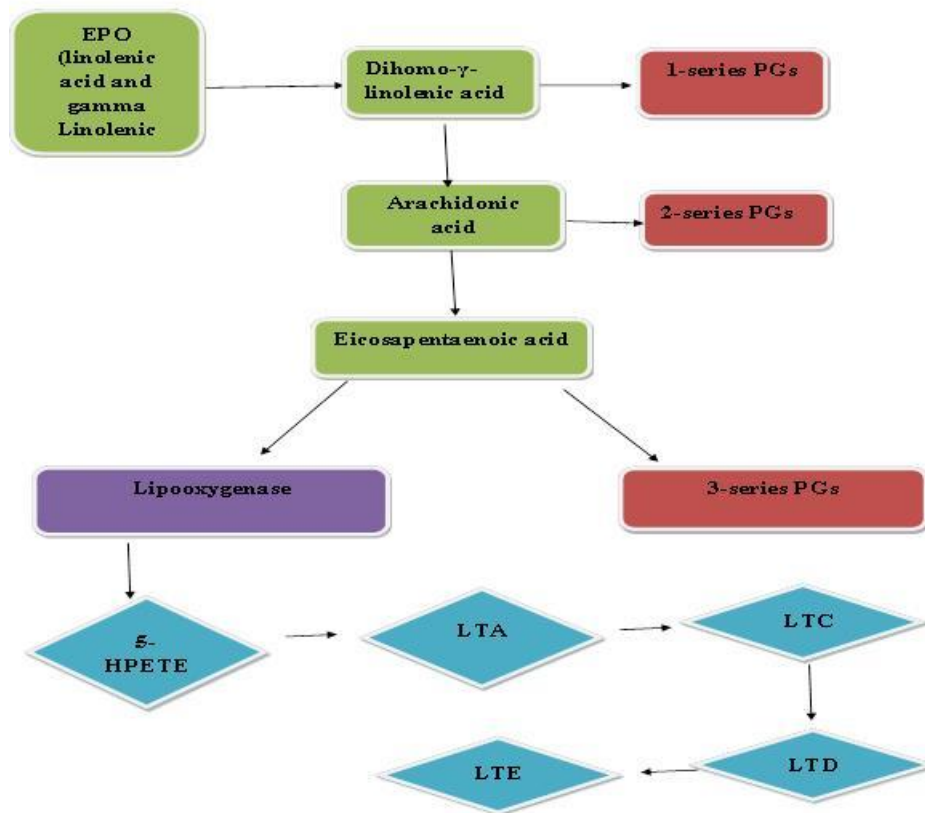
Herbal treatment is more consistent and less compliant with the human body, because drugs are natural. The new treatment for cyclic (premenstrual) and non-cyclical breast pain relieve by using in Evening Primrose oil. Evening Primrose oil appears to be the first line of management of moderate mastalgia without any adverse effects. The effectiveness of EPO in moderate to severe mastalgia is, however, uncertain (Sarayloo et al. 2017).

prostaglandin hormone and also leads to the conversion of Eicosapentaenoic acid (which secretes Lipooxygenase and 3-series PGs). 5-lipoxygenase (5-LO) catalyzes oxygenation of arachidonic acid (AA) to 5(S)-hydroperoxy-6-trans-8,11,14-cis-eicosatetraenoic acid (5-HPETE), and then leads to the further dehydration to the allylic epoxide leukotriene A₄, LTA₄ is further converted by LTA₄ hydrolase to the dihydroxyacid LTB₄, and by LTC₄ synthases to the glutathione conjugate LTC₄. The other cysteinyl-LTs are formed by hydrolytic removal of γ-Glu and Gly from LTC₄ (yielding LTD₄ and LTE₄). In proinflammatory contexts, LTs typically stimulate cellular responses, which are quick in onset and of short duration (as smooth muscle contraction, phagocyte chemotaxis, increased vascular permeability).

Mechanism of action of epo in human body and its conversion in prostaglandis

Linoleic acid, is breakdown in a compound dihomο-γ-linolenic acid(very crucial component of neuronal membrane phospholipids and as a substrate for the formation of PGE has important function in preserving nerve blood flow, this element then then converted into Arachidonic acid which is very important for the production of

Mechanism of EPO in human body and its conversion in prostaglandis



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Management of premenstrual syndrome

Premenstrual syndrome is linked with multiple problems such as emotional disturbance, somatic and behavioral problems includes commonly food sculping, irritable bowel movement, inflammation, nausea, insomnia, inflammation, exhaustion and headache. The symptoms of pre-menstrual dysphoreal disorders include insomnia and suicidal thoughts during luteal cycle phase, and are over 150 clinical symptoms such as behavioral, psychology and physical. The low

level of prostaglandin E1 induces high susceptibility to prolactin due to deficiency in essential fatty acids, which generates during ovulation and raises the peak amount during the luteal phases(Wang et al. 2018).

In a randomized placebo-controlled experiment, the fourth edition (DSM-IV-TR) text revision guidelines in EPO were tested on 80 women with PMS. A randomized dosage (1.5 g EPO) or placebo for three months showed that primrose oil is effective and safe for evening treatment in menstruation(Mahboubi, 2019b).

EPO is rich in fatty acids, such as γ -linolenic acid. Polyphenolic compounds, such as gallic acid and catechins, which may have antioxidant effects, are also present. A double blind randomized study of 40 women (ninety primrose, vitamins B6 and E) found that the primrose at night has been significantly alleviated in the PMS symptoms. The placebo tests for two menstrual cycles have been performed (Dietz et al. 2016).

Masoumi et al in 2017 conducted a double blind clinical trial on 70 volunteers from Imam Hossein health centers in Hamadan, Iran to compare the effects of vitamin E oil (400 IU) and EPO (1000 mg) on premenstrual primrose in the evening. The effect of evening primrose oil in the symptoms of premenstrual was better than the drug Vitamin E (Masoumi et al. 2017). Another study showed the protective effects of omega-6, comprising linoleic acid and γ -linoleic acid present in EPO. Results showed that treatment is effective for women's health, but not immediately and can only be used for 4 to 6 months every day daily (Mahboubi, 2019a).

Shayan and his colleagues in 2019 performed a study on 120 students of the Hamadan University of Medical Sciences premenstrual syndrome to compare the effect on the severity of premenstrual syndrome symptoms of the Evening Primrose capsule and vitamin B6 and placebo. EPO treatment decreased the severity of symptoms in PMS and limited side effects was observed and results also concluded that it can be useful in women with premenstrual problems struggling to conceive. In addition to vitamin B6 and placebo, a primrose capsule significantly lowers the effects of premenstrual syndrome (Shayan et al. 2019).

Combined effect of EPO 500 mg (73% cis-inoleic acid, 9% gamma-inolenic acid and 18% other fatty acids) along with vitamin E 13.6 IU was supported for the treatment of PMS. Improvements in depression and anxiety, regardless of the quality of medicines. An active therapy skin reaction (8 women) has been reported. None of the essential fatty acids nor placebo decreased PMS (Fisher, 2019). A Randomized, double blind, placebo controlled, parallel group comparison over two menstrual cycle on 76 women suffering premenstrual syndrome, aging 18-40 showed that significant improvement in the PMS (Fallah and Khaledian, 2008). A single blinded trial of EPO on women age between 18-40 years of age suffering from tenderness and breast pain in the Isfahan 2007, assessed by the Cardiff chart showed that EPO

reduced the severity of the pain and also concluded that it's better than vitamin E (Fathizadeh et al. 2008).

EPO protective role in mastalgia:

Paying attention to women's health is important. The majority of women usually suffer from mastalgia or breast pain is the most common symptoms among women of reproductive age a. (Sarayloo et al. 2017). The mastalgia cycle variant is prevalent, and patients need to be assessed and appropriately handled to alleviate their two main concerns: firstly the severity of the pain that affects everyday life, and secondly the fear of malignancy. The 70 per cent women in some phases of their life complain regarding breast pain. Mastalgia or breast pain in ladies in reproductive ages is a common distressing illness. During menstrual cycles, cyclic breast pain is triggered by changes in the hormone, whereas non-cyclical breast pains are not associated with menstrual cycle (Ooi and Pak, 2020). EPO have the ability to restore the fatty acids balance (saturated and unsaturated) and have been showed to decrease the sensitivity of steroidal hormones and prolactin. Balci and his fellows recently conducted a study on 1015 patients with mean age 42.21 ± 10.8 treated with EPO (1300 mg, twice a day). Results showed that EPO is significant therapeutic agent in treating mastalgia (Balci et al. 2020b).

Another retrospective case-controlled study included 1327 female patients with mastalgia compared the effectiveness of EPO treatment for mastalgia suggested that 1300mg EPO taken orally twice daily can be used successfully for mastalgia treatment, without significant adverse effects and strengthens the association of thyroid dysfunction with mastalgia (Balci et al, 2020a)

A double blind trial on 80 patients of cyclical mastalgia were treated by bromocriptine/evening primrose. Both group showed significant results but laser treatment covered more area as compare to drug treatment (Ied et al. 2007).

A 6 month double-blind, randomised, placebo-controlled trial combined effects of vitamin E (1,200 IU daily), EPO (3,000 mg every day), vitamin E (1,200 IU daily), plus OPE (3,000 mg daily), or double placebo (1,200 IU every day) in 85 women with cyclic mastalgia were enrolled in cyclical premenstrual lethargy. Change in breast pain measured by the modified McGill Pain Questionnaire during registration. Two results from two studies indicated a reduction in cyclic mastalgia from the non-important placebo

community in the three populations (EPO = 0.18; vitamin E = 0.10; and EPO + vitamin E = 0.16). The findings were also evaluated through the Aickin Trennung Experiment which revealed an independent and cyclic mastalgia tendency to reduce vitamin E and EPO. The severity of cyclical mastalgia can be reduced at six months in the same doses by a daily dose of 1,200 IU vitamin E or 3,000 mg EPO (Pruthi et al. 2010).

In an open, non-randomized comparative trial in the Department of General Surgery Iftikhar and his fellows investigated the effectiveness of Danazol and Evening Primrose (OEP) oil in Mastalgia. Patients with distinct swelling, nipple discharge, lumps, lactation, abortion and breast abscess were omitted from the analysis in and after the Cardiff Breast Pain Score (CBS) treatment. Danazol provides reasonable mastalgia pain control but has disquieting side effects while Evening Primrose Oil (OEP) has also shown good pain. Controls group have side effects without a lot of distress. The Danazol patients had 32% discomfort but reversible side effects compared with 12% in Oil of Evening Primrose, which are both unpleasant and reversible. Danazol has good mastalgia control but has distressing side effects, while EPO showed good pain control with minimum noticeable side effects (Iftikhar et al. 2019).

Another study was carried out on 90 patients complaining of breast periodic pain in Iran as a quasi-randomized clinical trial in 2015. One group got 30 g of flaxseed powdered. Two 1000 mg capsules of night primrose had been obtained in the second category and one 400 IU capsule Vitamin E had been obtained every day and for two menstrual cycles. The average breast pain duration in the flaxseed group decreased significantly in 2 months after the intervention. However, the Vitamin E capsule did not reduce the pain despite a decrease in the duration of pain in the primrose group. The level of significance was set at $P < 0.05$. Total, the average duration of breast pain before and two months after the treatment was not significantly different for all three flax seed oil groups (CI = 95%, $P = 0.667$). The analysis revealed that flax seeds can reduce breast pain (Jaafarnejad, Adibmoghaddam, Emami, & Saki, 2017)(Jaafarnejad et al. 2017). EPO improved the postmenopausal women's psychiatric symptoms with no side (Sharif and Darsareh, 2020).

In 128 mastalgic women combined effects of primrose oil, Fructus Agni Casti and mastalgia

showed high rate of effectiveness and a reduced profile of adverse effect (Kılıç et al 2016)

In the triple-blind trial with a control group, Evening Primrose and Vitex Agnus were used. In the first category, the mean pain parameter was $5/67 \pm 1/411$ prior to the intervention and $4/51 \pm 0/864$ after the intervention. The findings revealed that ViteX AgNus has some beneficial impact on women's pain scale with Mastalgia and can also be used as an effective treatment tool. Pain is a mental perception and there is an important difference between people's sense of painful events and reactions. The findings indicate that Vitex Agnus impacts pain in women with Mastalgia significantly and should be used as a treatment tool (Seraji et al 2014a). A single blinded trial of EPO on women age between 18-40 years of age suffering from mastalgic pain in the Isfahan 2007, assessed by the Cardiff chart showed that EPO reduced the severity of the pain and also concluded that it's better that vitamin E (Fathizadeh et al.)

In 2012 Sharma and his fellows found the no effect of 3g/d EPO on mastalgic pain instead 30 mg centchroman elicits weak estrogen agonistic and strong antagonistic activities and is devoid of progestational, androgenic, and anti-androgenic activities (Sharmat et al. 2012). In another quasi-randomized study conducted on 90 women received 30 g of powdered flaxseed, the second group received two 1000 mg capsules of evening primrose, and the third group received 1 capsule of 400 IU Vitamin E, daily and for two menstrual cycles in Gynecologic Clinics of Ghaem Hospital or residents living in dormitories of Mashhad University of Medical Sciences. The use of flaxseed showed significant reduction (Jaafarnejad et al., 2017).

Nigham et al in 2019 showed no effect of 1000mg EPO in the treatment of mastalgia but the 30mg ormeloxifene visual analogue scale of pain (VAS) score in first month was much more with ormeloxifene than with evening primrose oil. Ormeloxifene is more effective than evening primrose oil in long term in the treatment of mastalgia. (Nigam et al. 2019). A triple-blind trial studied the effects of evening primrose and vitex agnus on pain scale of the women with cyclic mastalgia a clinical trial showed that demonstrated that Vitex Agnus has some positive effects on the pain scale of the women's with Mastalgia and thus can be used as an effective clinical method. (Seraji et al. 2014b)

A prospective clinical study on the effectiveness of evening primrose oil, Fructus

Agni Casti and reassurance in the treatment of mastalgia 128 female patients with mastalgia. Fructus Agni Casti can be used in mastalgia patients with a high success rate and less adverse effect profile. Reassurance may be an important part of mastalgia management, due to the psychological basis of this entity.(Kılıç et al. 2016).

Management of menopause and hot flashes

The World Health Organisation (WHO) says that evening primrose oil has many advantages in treating menopause, which is defined as a longer-lasting menstruation termination due to hormonal and physiological changes involving the loss of the follicular activity of the ovaries. It typically takes place between the ages of 40s and 50s(Johnson et al. 2019).There are a number of causes that may lead to the onset of menopause, including natural hormone declines caused by ageing, surgical operations, chemotherapy, radiation and other conditions such as premature ovarian failure (Kazemi et al. 2021). It has psychological synthesis (mood swings, anxiety, depression), bony-like aches, hard sleep, eczema and urogenital symptoms (vagina, dyspareunia, urinary frequency and emergency), and is characterized by vapour motor symptoms e.g. heavy-duty flushes and bones (Nouri et al. 2021).

Sharif and Darsareh recently conducted an 8 week 1000 mg EPO supplementation based double-blinded randomized placebo-controlled trial. Only 1 patient reported gastric complain and significant improvements was seen in the after intervention in the psychological score of post-menopausal women (Sharif and Darsareh, 2020)

Another triple-blind clinical trial showed visible reduction in post-menopausal symptoms (sleep disorders, hot flushes, musculo-skeletal disorders as compared to placebo group with 1g of EPO twice a month among 100 postmenopausal women(Motaghi and Karimian, 2017)

Approximately 74 to 80% of females worldwide are affected by menopause symptoms, e.g. by night sweats, sleep disturbance, heart problems and flushing. The hormone replacement method is used as treatment, which has serious side effects. Another alternative way to substitute hormones is the use of plants from the phytoestrogens family, such as evening primrose. Results of the study indicated that evening primrose has a significant effect on flushing reduction (3.33 ± 0.79 vs. 0.89 ± 0.64), sleep and musculoskeletal disorders in the primrose compared to the control group. It may be

used to improve its symptoms, as a complementary therapy or as a substitute for hormone (Motaghi et al. 2017).

Hot flashes are characterized as a quick sensation of intense warmth in the chest, which begins with sweat and refreshment on the neck and face. Palpitations are not unusual and fearful. The duration of hot flashes is unpredictable, which can happen many times a day. Hot flashes will affect the job, exercise, sleep and quality of life of woman. The loss of estrogen appears to trigger hot sweats, but neuroendocrine reliable mechanisms are not yet clear. Hormonal replacement therapy is a popular type of management for the effects of menopause. The risk of HRT was, however, increased, and adverse cardiovascular effects were associated with it. EPO is the most common medication for 1,296 menopause women in Sydney as a complementary and herbal medicine. Women 66.3 percent thought that menopause problems were treated effectively. Hot flash is the most common symptom of menopause (van der Sluijs and Shah, 2007).

Farzaneh et al. in 2013 conducted a six-week randomized clinical trial on 56 menopausal women from 45 to 59 years of age. The intensity, frequency and length of the hot-flash change in the evening primrose group. While in the evening primrose arm all three characters of the hot flash were improved, its severity in this arm was only significantly better than in the placebo group. In two groups, all HFRDIS scores were substantially improved. A substantial percentage increase was higher than the placebo category in social interactions, relationships with others and attractiveness ($P<0.05$) (Farzaneh et al. 2013).

An 8 weeks study compared the efficacy of EPO and black cohosh in 80 menopausal women with hot flashes. The two plants have decreased flash heat and boost quality of life efficiently, but black cohosh appears to be more productive than primrose oil, as it was able to minimize hot flashes (Mehrpooya et al. 2018).

A triple-blind clinical trial tested 100 postmenopausal women sent to the health centers in Dastena in 2015. The two groups included in study of placebo and evening primrose. The Kuperman questionnaire was used to identify symptoms of menopause. Results indicated significant decrease in the frequency, length and frequency of the hot flashes at night in contrast with placebo ($P<0.001$) concluded that it can be used as a supplement or hormonal

substitution therapy to relieve the effects of menopause in women (Motaghi et al. 2017).

Management of cervical ripening and dilatation

EPO is the most suggested midwives as it has most the ability to help cervix ripening, stimulation of labour, preventing postdate pregnancy and shortening the interval of labour. Certified Nurse-Midwives in the United States felt EPO is the utmost successful herb and scored high on their "comfort level in prescribing scale."1 as it contains high amount(GLA), a very active essential fatty acid and a precursor of prostaglandin derivatives (Beites and Dugoua, 2010). EPO with prostaglandin (E1 and E2) precursors had relaxant activity on smooth muscle, which changes cervical vascular tone and consistency, the cervical dilation (Hall et al. 2012)

In thirteen patients mean age(27 ± 6 years) and a mean gestation period(40 ± 1) weeks, the efficacy of the evening primrose oil capsule 500mg as a cervical ripener was tested with a Bishop score evaluation before and 4 hours after the intervention. 85% improvement was seen in Patients the cervical dilations and eradication in patients. Patients with 31% had vaginal delivery, while 69% had cesarean section, including fetal-non reassurance (46%), cervical dilation arrest (15%), and intra-amniotic infection (8%) (Nonette, 2017).

Vahdat et al in 2015 evaluated the 500 mg of primrose oils per night for cervical maturation and expansion in 36 non-menopausal patients and 14 menopausal patients. The use of evening primrose oil reduced the entire time of cervical dilation. In the evening, primrose oil also caused higher initial cervical dilation or strength for cervical dilation compared to the placebo group. No adverse effects or symptoms of the cervical uterus during the study were identified (Vahdat et al. 2015).

DeGolier and Ortmann in 2017 investigated the effects of 1000 mg EPO on dilation of cervix and pain on 66 female of Hysterosalpingography in a double-blind clinical trial of associated with allergic sensitivity, pain, abdominal cramps and shock. The Visual Analogue Scale (VAS) evening primrose seems to be a good drug for managing pain during hysterosalpingography (DeGolier et al. 2017).

The cervical ripening effects of EPO observed by Tanchoo et al (2015) showed that EPO showed no pain and easy cervical dilation with less time was as compare to luminaria suggested

that EPO may be used prior to childbirth or hysteroscopy .

EPO(1000 mg) in triple blind placebo controlled randomized clinical trial on 80 women with a gestational age of 40 weeks twice daily for 7 days showed no significant difference(Kalati et al. 2018) A retrospective quasi-experimental design conducted showed EPO from the 37th gestational week until birth associated with an increase in the incidence of prolonged rupture of membranes, oxytocin augmentation, arrest of descent, and vacuum extraction(Dove and Johnson, 1999).

An in vitro study investigated that EPO increased the force of uterine contractions, these contractile forces were slightly greater than those evoked from acetylcholine (10^{-5} M). Cervical tissues that were pre-contracted with a high potassium solution did not demonstrate any relaxation following 15 min incubations with the EPO. The β adrenergic receptor agonist isoproterenol did relax the cervical tissues by 97% (DeGolier et al. 2017).

EPO 4 capsules intra-vaginally, 6 hours prior to the contemplated procedure on 80 patients given in a tertiary care hospital study scheduled for gynecologic procedures Concluded that EPO can promote cervical ripening as exhibited by the improvement of the Dilation Index from initial assessment to pre-procedure assessment (Girlye, 2015). comparative effects of 500 mg EPO and Misoprostol on Cervical Ripening of Nulliparous Women with Post-term Pregnancy showed vaginal capsule of evening primrose oil with misoprostol on the cervical ripening in post-term pregnancies was more effective than misoprostol alone (Bahmani, Hesamy, Shahgheibi, Roshani, & Shahoei, 2019). The use of EPO in the 42 patients proved that Evening Primrose Oil can be used as a cervical priming agent prior to gynecologic procedures (Marian, 2009).

1000 mg EPO vaginal capsules from the 38th week of pregnancy until delivery given to the 86 nulliparous women who referred to the comprehensive health service centers of Rafsanjan from November 2017 to May 2018. Vaginal Evening primrose is effective to ripen the cervix of term nulliparous women and so, it could be administered for this purpose (Najafi et al. 2019). EPO improves dysmenorrhea, according to Atteia et al in 2019 5 or 10 g/kg EPO improved hyperleptinemia and reproductive hormone disturbances in obese female rats in 32 female rats. The underlying molecular mechanism may be related to reduction of systemic inflammation,

alleviating insulin resistance and modulation of adipokine expression. EPR oil may be considered as a promising therapeutic intervention against obesity-related female hormonal disturbances and estrus irregularity (Atteia et al. 2019). Another randomized, double-blind, placebo-controlled trial included a total of 42 patients here was a statistical and clinically significant difference between the initial cervical dilatation in the treatment proved that Evening Primrose Oil can be used as a cervical priming agent prior to gynecologic procedures (Bahmani et al. 2021).

CONCLUSION

This review concluded that EPO has significant therapeutic effect on mastalgia, premenstrual syndrome, hot flash, menopause and cervical maturation. There is still need to understand the mechanism of action of EPO, for in depth exploration on further female elements to determine its efficacy as a dietary supplement and therapeutic.

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CONFLICT OF INTEREST

The authors declared that present study was performed in absence of any conflict of interest.

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AUTHOR CONTRIBUTIONS

MA and BR conceptualized, supervised the study, data collection, results interpretation, review, rewrite final manuscript, design of the work, and results interpretation. SB and MA, SB and AA conceived and analyzed the presented idea, works on methodology, data analysis and interpretation. AA, ZF, FR and AAS works on drafting of article.

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