

The Use of Flaxseed in Gynecology: A Review Article

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ABSTRACT

Background & aim: Flaxseed is the richest source of lignan which is one of the main categories of phytoestrogens. In addition to the estrogenic and anti-estrogenic properties of lignan, it has non-hormonal properties as well. The treatment of menopausal hot flashes and cyclic mastalgia, the reduction in vasomotor symptoms and tumor cell growth and recurrence, the prevention of breast and ovarian cancer, and the improvement of the symptoms of premenstrual syndrome are some of the indications of this plant. Therefore, the current study aimed to review the effect of flaxseed on the control of menopausal symptoms, premenstrual syndrome as well as breast and ovarian cancers.

Methods: In this study, English keywords of mastalgia, mastodynia, ovarian neoplasm, ovarian cancer, breast neoplasm, breast cancer, hot flashes, premenstrual syndrome, flax, flaxseed, lignan, phytoestrogen, and *linum usitatissimum* along with their Persian equivalents were searched through databases including PubMed, Proquest, Scopus, Science Direct, Google Scholar, SID, and Magiran. All the selected articles were the clinical trials and case-control studies performed from 1991 to 2017. Finally, 30 English and 8 Persian studies were reviewed in this study.

Results: The results obtained from most studies on this plant showed its positive effects on menopausal symptoms, breast cancer, mastalgia, and premenstrual syndrome.

Conclusion: According to the results, it can be concluded that due to the high properties of this plant (i.e., the negligible side effects and safe use of it in recommended amounts), it can be used within the field of obstetrics and gynecology.

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Introduction

Flax is an annual herb which is cultivated in tropical and temperate regions. Flaxseed is an important component that has biological properties (1). Flaxseed with a scientific name of *Linum Usittatissimum* is often used as a dietary supplement (2, 3), and it is the richest source of lignans and the main source of phytoestrogens (1). Each 100 g of flaxseed contains 60-300 mg

lignans (4). The most important lignan in flaxseed is secoisolariciresinol diglucoside (SDG) that is converted to the active biological form (i.e., enterodiol and enterolactone) by intestinal bacteria which is a weaker estrogen, compared to estradiol (2, 5). Flaxseed also contains small amounts of matairesinol lignin (6). Other compounds in flaxseed include

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essential fatty acid (i.e., the alpha-linolenic acid, a biologic precursor of omega-3 fatty acids) and fiber (1). Phytoestrogens are not synthesized or stored in the human body; therefore, the only source is an herbal diet containing these substances (7).

Flaxseed has diphenolic compounds that are structurally similar to endogenous estrogens. Lignans are found in many herbs, such as whole grains, grains, coffee, tea, vegetables, and legumes. However, the amount of lignans in flaxseed is 100 to 800 times more than that found in other foods (2, 8). Lignans have estrogenic and anti-estrogenic hormone properties in addition to antioxidant, anti-angiogenic, antiviral, antifungal, and anti-inflammatory non-hormonal properties (8-10). Flaxseed compounds contain approximately 30% fiber, 20% protein, 40% fat, 4% ash, 6% moisture, and 4% lignans (11). Flaxseed can be used in many different ways. The results of most studies have shown that flaxseed can be effective in the treatment of menopausal hot flashes. High levels of phytoestrogens available in flaxseed lead to the increase of estrogen levels and hormonal imbalance. Therefore, it reduces the frequency of other vasomotor symptoms (1, 7).

Moreover, it contains lignans with potent anti-estrogenic effects on breast cancer, and may help prevent breast, uterine, and other hormonal-associated cancers and their recurrence. It has even been reported effective in the reduction of the tumor growth among patients with breast masses (1, 3, 6, 8, 11). Flaxseed is introduced as the first-line treatment of the cyclic mastalgia (3) because of the omega-3 fatty acids which relieve the symptoms of premenstrual syndrome (12).

The seeds of this plant have been used in the treatment of diseases, such as upper respiratory infections, constipation, abdominal pain, urinary tract infections, and skin inflammation (6). Some studies have proved the desired effect of flaxseed and its derived lignans on the level of C-reactive protein and blood lipids, such as total level of cholesterol, low-density lipoproteins, and triglycerides (3). The desired effect of this plant on cardiovascular markers and diabetes has been observed in other studies (13). Flaxseed has a fluidizing effect due to the presence of mucilage fibers and increased

volume and stimulation of the peristaltic movements (6). Accordingly, the German Commission E has confirmed the use of flaxseed in chronic constipation, colon damage caused by laxatives, irritable bowel, diverticulitis, and intestinal infections (6).

Flaxseed has anti-oxidant properties due to the presence of SDG lignin. Moreover, eicosapentaenoic and docosahexaenoic acids inhibit neutrophilic inflammatory responses in humans leading to anti-inflammatory responses. Other effects of flaxseed include decreased platelet aggregation (6). Flaxseed has many potential therapeutic benefits for the treatment of women's diseases; however, no study has been done so far on the use of this plant in this regard. Therefore, the current review article provides evaluations on flaxseed application in the field of obstetrics and gynecology, such as menopausal symptoms, premenstrual syndrome, and breast and ovarian cancers.

Materials and Methods

In this study, the English keywords of Mastalgia, Mastodynia, Ovarian Neoplasm, Ovarian Cancer, Breast Neoplasm, Breast Cancer, Hot Flashes, Premenstrual syndrome, Flax, Flaxseed, Lignan, Phytoestrogen, and *Linum Usittatissimum* along with their Persian equivalents were searched through such databases as PubMed, Proquest, Scopus, ScienceDirect, google scholar, SID, and Magiran. All the selected articles were the clinical trials and case-control studies performed from 1991 to 2017. Finally, 30 English and 8 Persian studies were assessed in this study (Table 1).

Flaxseed and Hot Flashes

Flaxseed can alleviate hot flashes and vasomotor symptoms (1, 7). Hot flashes are classic menopausal symptoms that persist for 2 years or longer (1) in more than 70% of the women in the mid-life (14). Although exogenous estrogen is effective in the reduction of menopausal symptoms, most women are not interested in the treatment with estrogen. On the other hand, hormonal treatment is contraindicated among many women. Only 20% of postmenopausal women use hormone therapy and its use is rapidly stopped due to the fear of side effects, especially breast cancer

(5, 15). Interest in complementary medicine, especially plant sources, has been increased in

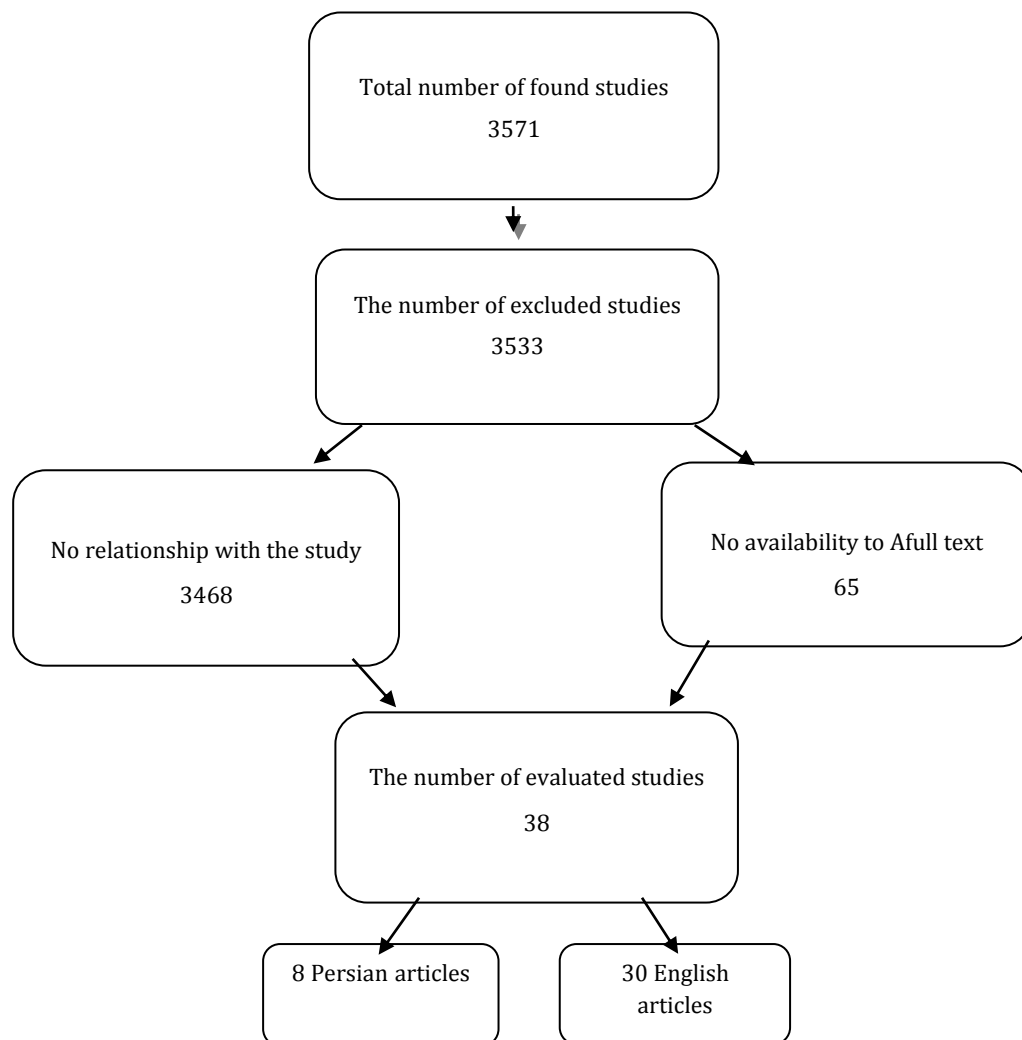


Figure 1. Process of the review study

recent years to reduce the symptoms of menopause (15). Women are more tended to use flaxseed than soybean derivatives (as a rich source of phytoestrogens) (16). Many women use flaxseed as a rich source of lignan phytoestrogens (8) because it reduces the symptoms of menopause (17). In Japan, it is estimated that phytoestrogens are used 200 mg per day. Therefore, the incidence rates of hot flashes, estrogen-dependent cancers, and osteoporosis are lower among Japanese women, compared to those in other parts of the world

(17). The structure of lignan diphenolic and phytoestrogens is similar to 17 beta-estradiol, which has estrogenic or anti-estrogenic properties based on estrogen circulation levels.

flaxseed acts as an agonist in the menopausal period when the estrogen level is low (15). Many studies evaluated the effect of flaxseed on the symptoms of menopause and hot flashes. The results of Cetisli et al. (2015) study on 140 postmenopausal women showed that flaxseed consumption as 5 gr per day for 12 weeks significantly decreased the menopausal

symptoms. Similar results were observed in the hormone therapy group in which flaxseed consumption resulted in a decrease (10%) in menopausal symptoms (7). In the study of Pruthi et al. (2012), 188 postmenopausal women with and without breast cancer were randomly assigned into a group of 7.5 gr flaxseed (containing 410 mg lignan) for 6 weeks and a placebo group. The results showed that flaxseed and placebo similarly reduced the hot flashes; however, the findings did not support the role of lignans in the alleviation of hot flashes (1).

In the study conducted by Colli et al. (2012), 90 postmenopausal women were randomly divided into three groups. The first group received two 500 mg capsules containing 1 gr of flaxseed extract (50 mg lignan) daily. The second group received two spoons of 90 gr flaxseed daily, and the third group received two 500 mg capsules containing 1 gr of collagen (placebo) daily for 6 months. The menopausal symptoms were measured using the Kupperman Index at the beginning and at the end of a 6-month intervention. Both flax extract ($P=0.007$) and flaxseed ($P=0.005$) were more effective than placebo ($P=0.082$) in the reduction of menopausal symptoms. However, it was not statistically significant ($P = 0.084$).

The intensity of hot flashes significantly decreased in flax extract group ($P=0.001$) and flaxseed ($P=0.035$), whereas it was not significant in the placebo group ($P=0.231$). The findings of this study showed no clear conclusion about the effect of flaxseed on menopausal symptoms (18). Another study by Torkestani et al. (2012) was a double-blind clinical trial which was performed on 90 postmenopausal women with hot flushes. Individuals were randomly assigned into one of three groups of 25 gr flaxseed, 25 gr soybean, and 25 gr wheat flour daily for 8 weeks.

The results showed that flaxseed and soybean reduced the frequency and severity of hot flashes among postmenopausal women. In terms of reduced frequency of hot flashes at the end of the study, the soybean group had more reduction than the other groups (19). The study of Torkestani et al. (2011) was a triple-blind randomized clinical trial which was performed on 60 postmenopausal women with hot flushes.

In this study, the subjects were divided into two groups. The first group received 6 gr fenugreek seeds daily and the second group received 25 gr flaxseed powder daily for 4 consecutive weeks.

Both flaxseed and fenugreek seeds reduced the severity and frequency of hot flashes among postmenopausal women; however, the reduction was not statistically significant ($P=0.12$). While in the flaxseed group, the reduction in terms of the intensity of hot flashes was significant after the eighth week ($P=0.028$); however, it was not significant after the fourth week (10).

Baghdari et al. (2011) conducted a double-blind cross-over clinical trial on 62 postmenopausal women who suffered from hot flashes. Individuals were randomly divided into two groups of 40 gr flaxseed or wheat flour daily for 6 weeks. After the washout period, the place of subjects was changed. The results showed that flaxseed significantly decreased the severity and duration of hot flashes, compared to the placebo group ($P=0.009$ and $P=0.045$). However, no significant difference was observed between the flaxseed and placebo groups in terms of the frequency of hot flashes ($P=0.23$). In subjects who had the frequency of hot flashes less than 7 times at the beginning of the study, flaxseed powder showed a significant decrease, compared to the placebo group ($P<0.01$). The severity of night sweats and sleep disturbance reduced more in the intervention, compared to the placebo group ($P=0.005$ and $P=0.028$). Moreover, no significant difference was observed between two groups in terms of the frequency of night sweats ($P=0.46$). However, the effect of flaxseed powder was more among subjects who had the frequency of night sweat less than 2 times or less at the beginning of the study, compared to those in the placebo group ($P<0.001$)(16).

Simbalista et al. (2010) performed a double-blind placebo-controlled randomized clinical trial on 38 postmenopausal women who daily used two pieces of bread containing 25 gr flaxseed (46 mg lignan) or wheat bran (less than 1 mg lignin) for 12 consecutive weeks. There was a significant reduction in vasomotor symptoms and frequency of hot flashes within both groups. However, a decrease in the intensity of hot flashes within the flaxseed group

was not more than that within the placebo group. Moreover, no significant difference was observed between the two groups after 12 weeks of intervention (5). Pruthi et al. (2007) performed a study on daily use of 40 g flaxseed for 6 weeks on 28 postmenopausal women with hot flashes. The hot flash scores and hot flash frequencies reduced by 57% and 50%, respectively in the flaxseed group. This study showed that treatment with flaxseed supplement reduces hot flashes among women who were not treated with estrogen. This reduction was more in the intervention, compared to the placebo group (20).

In the study by Lewis et al. (2006), 99 postmenopausal women used candies containing 25 gr flaxseed (50 mg lignan), 25 gr soybean muffins (42 mg isoflavone), and wheat flour muffins (control) daily for 16 weeks. The results showed a significant difference in the intensity of hot flashes not its frequency in the flaxseed group ($P=0.001$) (15). In a randomized clinical trial with a placebo control group which was conducted by Dodin et al. (2005), 179 women consumed 40 gr flaxseed (21 mg lignan) for more than one year at multiple times. The results showed that flaxseed did not reduce hot flashes much more than the wheat flour (21). In a small randomized clinical trial, Lemay et al. (2002) evaluated the effect of estrogen+/- progesterone flaxseed diet on lipids among 25 women with menopausal symptoms. In this study, 40 mg flaxseed (21 mg lignan) versus 0.625 mg conjugated estrogen was used daily for 2 months. The results showed that both drugs were effective in the significant reduction of menopausal symptoms (22).

The results of the study by Dalais et al. (1998) on 52 postmenopausal women showed that the frequency of hot flashes significantly decreased in flaxseed and wheat (placebo) groups. However, no significant decrease was observed within the soybean group during the two cycles of 12 weeks of intervention (23). According to the performed studies, the majority of findings show the positive effect of flaxseed on menopausal hot flashes. Therefore, it can be recommended for the treatment of hot flushes among women who are suffering from menopausal syndromes.

Flaxseed and Breast cancer

Breast cancer is one of the most common concerns of women which is diagnosed as the most prevalent cancer among females in Western societies (4, 11, 24, 25). In addition, million new cases are added annually (26). The mortality rate of this cancer has decreased due to the improvement in screening, early detection, and treatment. However, breast cancer is still the second leading cause of cancer-related deaths (11). This multifactorial disease includes unchangeable risk factors, such as early menarche, late menopause, family and genetic history. On the other hand, the changeable factors include diet, lifestyle, alcohol consumption, use of hormone therapy, radiation exposure, physical activity, and breastfeeding (11, 27). Despite the wide screening and progressed auxiliary treatments which lead to early diagnosis and longer survival, the breast cancer burden is very high. As a result, the survivors of breast cancer are interested in moderators which improve the disease-free survival. Anti-estrogen therapy is a standard treatment in receptor-positive breast cancer (2). In addition to pharmacological agents, alternative and complementary approaches are widely used among breast cancer survivors. They attempt to prevent the recurrence of breast cancer, reduce the number and the severity of side effects, and provide potential benefits (2). The estrogen is one of the causes associated with breast cancer. Lignans can affect the risk of breast cancer by modifying endogenous estrogen metabolism or competing with estrogen receptors (9).

Flaxseed is an oilseed which is rich in n-3 polyunsaturated fatty acid, alpha-linolenic acid, and phytoestrogens of lignans. Patients with breast cancer use the therapeutic benefits of flaxseed to improve the treatment and prevent recurrence (11). The protective effect of flaxseed on breast cancer has been observed among animal and epidemiological studies. The results showed the effects of flaxseed on the prevention and treatment of cancer (8). Laboratory studies have shown that in the presence of estrogen, lignans inhibit the growth of cells in the type of estrogen-dependent breast cancer (8). Moreover, the results of most studies on rodents show that a diet containing 2.5-10%

flaxseed or lignin decreases tumor growth (11). The consumption of fiber has an inverse relationship with breast cancer. In the group of women who consumed a high-fiber diet such as flaxseed, there was a reduction in the risk of recurrent breast cancer (28).

Due to the structural similarity of lignans with estradiol and selective estrogen receptor modulators such as tamoxifen, this substance is commonly used in the treatment of breast cancer (8). Lignans reduce breast cancer and the associated mortality by 33-70% and 40-53%, respectively, without a decrease in the effectiveness of tamoxifen (11). Phytoestrogens prolong the menstrual cycle follicular phase and reduce the production of endogenous estradiol and possibly the proliferation of breast cells. On the other hand, phytoestrogens suppress tumors through non-hormonal pathways, such as anti-oxidant activity, apoptosis, angiogenesis, or the inhibition of growth factors and tyrosine kinase (29). With regard to human and experimental studies, it has been shown that flaxseed is effective on both pathways of endocrine and growth factors, insulin-dependent growth factor, epidermal growth factor, and the inhibition of aromatase and 17 beta-hydroxysteroid dehydrogenase through modulation of steroid hormones metabolism.

Lignan inhibits cell proliferation in estrogen receptor-positive and estrogen receptor-negative human as well as animal cells leading to the reduction in tumor growth. Moreover, Lignan metabolites and its combination with tamoxifen, as synergism, decreases the tumor growth (2). Although the results of epidemiological studies are uncertain, several studies have shown that phytoestrogens are associated with a reduction in the risk of breast cancer. However, some studies have shown no significant relationship between phytoestrogens and the reduction in tumor growth (30-32). Most studies have shown that lignan use is associated with a decrease in the risk of breast cancer among women before menopause; however, in most studies, no significant correlation was observed regarding postmenopausal women (9, 32-35). McCann et al. (2014) conducted a study on 28 postmenopausal women with estrogen receptor-positive breast tumors. The participants assigned into 4 groups of 25 gr

flaxseed plus one placebo tablet per day, 1 mg anastrozole per day, 25 g flaxseed plus 1 mg anastrozole per day. In addition, the control group received one placebo tablet per day for 13-16 days. The results showed no effects of flaxseed on the inhibitory activity of aromatase followed by any influences on tumor characteristics and the level of steroid hormones (2).

A case-control study conducted by Lowcock et al. (2013) on 2999 women with breast cancer and 3370 healthy women showed that flaxseed significantly reduced the risk of breast cancer by about 20% to 30% (13). A clinical trial was carried out by Fabian et al. (2010) on 45 premenopausal women at high risk of breast cancer who used daily 50 mg secoisolariciresinol diglycoside for 12 months. According to the results, the median cell proliferation at the end of 12 months of the intervention decreased significantly by 50% and favorable changes were observed in the histological characteristics of the tumor. No changes were diagnosed by mammography in breast density, thereby indicating that short-term use of lignans had no protective effect (36). Cotterchio et al. (2008) conducted a case-control population-based study on 3063 women with breast cancer and 3430 healthy women. The results showed a decrease in the risk of breast cancer among non-menopausal women who used lignans.

Moreover, the significant effect of body mass index (BMI) was observed on the risk level of breast cancer. Therefore, with regard to the classification based on BMI, the reduction of risk was significant only in the group of overweight women (29). The results of a population-based case control study conducted by Fink et al. (2007) showed that isoflavone consumption was not associated with a reduction in the risk of breast cancer. However, the use of lignans among postmenopausal women decreased the risk of breast cancer. This reduction was not observed among women before menopause and was not related to estrogen receptor status (37). Moreover, Thanos et al. (2006) conducted a Canadian case-control study of 3024 cases and 3420 controls. The results showed an association between phytoestrogens consumption in

adolescence and a reduction in the risk of breast cancer in adulthood (38). The study of Thompson et al. (2005) on 32 postmenopausal breast cancer patients showed that daily use of 25 gr flaxseed from the time of the first biopsy to surgery reduced cell proliferation significantly and increased apoptosis. Furthermore, the results revealed a significant reduction in terms of gene expression in human breast cancer cells (8).

According to a population-based case-control study by McCann et al. (2004), the association between dietary intake of lignans and the risk of breast cancer was investigated on 1122 women with breast cancer and 2036 healthy women. In this study, the menopause status was effective on the risk of breast cancer in relation to lignan consumption. The risk of breast cancer decreased in premenopausal women who were in the highest quartile of lignan consumption. However, there was no relationship between lignan consumption and the risk of breast cancer among postmenopausal women. The results of this study supported the use of higher levels of lignans to reduce the risk of breast cancer, especially among premenopausal women (9). Another case-control study carried out by McCann et al. (2002) on 207 women with primary breast cancer and 188 healthy women. The results showed a significant protective effect of high levels of lignin on the risk of breast cancer, especially among premenopausal women (33). Horn-Ross et al. (2002) conducted a case-control study on 1326 women with breast cancer and 1657 healthy women. According to the obtained results, phytoestrogens were not associated with the risk of breast cancer even after adjusting the results in terms of menopause (39). In the evaluation of mentioned case-control studies and clinical trials, most studies pointed to positive effects of flaxseed on reducing the risk of breast cancer, especially among women who used this substance before menopause.

Flaxseeds and Mastalgia

People prefer to use herbal supplements in the treatment of chronic diseases, such as mastalgia (40). Mastalgia is the most common benign disorder of breast affecting women of reproductive age leading to midwife-led

counseling interventions (3, 41). Among all forms of mastalgia, cyclic mastalgia is the most common type that is observed among about 80% of women. It is often described as abnormal sensitivity and boredom heaviness of the breast (42). The main cause of cyclic mastalgia is unknown; however, its onset in the luteal phase can be a sign of breast parenchymal hormonal stimulation. Hormonal causes include increased levels of estrogen and prolactin, decreased levels of progesterone, and an imbalance in estrogen/progesterone ratio (3, 42). On the other hand, non-hormonal causes consist of nutritional factors, such as excessive intake of caffeine and high-fat diet as well as lack of essential fatty acids. This result in increased production of prostaglandins leading to breast pain, abnormal fluid retention, and psychological and medicinal disorders (43, 44). Hormonal and non-hormonal drugs are used to treat cyclic mastalgia. The adverse effects of using hormonal drugs have limited their use as the first line of treatment; however, the most appropriate drug is still not recommended due to the controversies with regard to the selection of most effective therapeutic method (45, 46). Herbal or dietary supplements, have a few side effects and are more popular than hormone-balancing supplements (40, 46). Flaxseed has been introduced as the first line treatment for cyclic mastalgia, due to its structural similarity to tamoxifen and aromatase enzyme inhibitors (3, 8, 47). There are limited studies which have been conducted on the effect of flaxseeds on cyclic mastalgia. Jafarnejad et al. (2016) carried out a study on 90 patients with cyclic mastalgia. According to the results, daily intake of flaxseed (30 mg), evening primrose oil (two capsules of 1000 mg), and vitamin E (1 capsule 400 Unit) for two menstrual cycles resulted in a reduction in the severity of breast pain. The reduction level was similar in all three groups; however, flaxseeds and evening primrose oil affected the severity of breast pain by one cycle of consumption (48).

On the other hand, the reduction in pain duration was significant only in the flaxseed group (49). The results of a study by Mirghafourvand et al. (2016) on 159 women with cyclic mastalgia showed that the

consumption of 25 gr flaxseed and 3.2 to 4.8 mg vitagnus tablets for two menstrual cycles was effective in reducing the cyclic mastalgia (50). Vaziri et al. (2014) conducted a study on 181 women complaining of cyclic mastalgia. The results showed that 30 gr flaxseed for two menstrual cycles reduced the severity of mastalgia more significantly than omega-3 fatty acid ($P < 0.0001$). Moreover, omega-3 fatty acids were also more effective than wheat bread as a placebo ($P = 0.003$) (3). In addition, Goss et al. (2000) in double-blind placebo-control trials on 116 women with severe cyclic mastalgia, showed a significant improvement in severe cyclic mastalgia after daily consumption of 25 gr flaxseed for 4 menstrual cycles (51). Studies on the effect of flaxseed on cyclic mastalgia are limited; however, all of the above trials have highlighted the positive effects of flaxseed on the reduction of cyclic mastalgia.

Therefore, flaxseed can be a suitable substitute for the drugs which come with many side-effects and used for the treatment of this disorder. Accordingly, more extensive studies with larger sample size and longer duration are required to determine the effect of flaxseed and the appropriate effective dosage in the improvement of cyclic mastalgia.

Flaxseeds and Premenstrual syndrome

Flaxseed has recently been used in the treatment of premenstrual syndrome. The premenstrual syndrome consists of a set of emotional, behavioral, and physical symptoms that occurs at least one week before menstruation. It decreases with the onset of menstruation or stops 4 days after the period. Many women experience premenstrual syndrome at reproductive age (50, 52). This syndrome causes significant disorders in everyday life activities, including work, school, social activities, hobbies, and interpersonal relationships (53). The main cause of premenstrual syndrome is unknown, although the role of hormonal and neurotransmitter factors has been suggested in the etiology of this syndrome (50). Some of the possible causes include genetic causes, lifestyle, deficiency of vitamins and minerals, and hormonal changes (54). About 80% of women with this syndrome

prefer to use acupuncture and herbal medicines (55). Flaxseed is reported as being effective in the alleviation of the symptoms of premenstrual syndrome (48, 56). Mirghafourvand et al. (2016) study is the first and only research which has already examined the effect of flaxseed on the symptoms of this syndrome. This clinical trial was conducted on 159 women with a triple-blind design. The participants were assigned into three groups receiving 25 gr flaxseed and vitagnus tablets (placebo), vitagnus tablets and flaxseed (placebo), and vitagnus tablets (placebo) and flaxseed (placebo) for two menstrual cycles. The results showed that flaxseed and vitagnus both were effective in reducing premenstrual syndrome (50). In this regard, further research is needed in order to achieve clearer conclusions.

Flaxseed and Ovarian cancer

Flaxseed, as a chemical precursor of breast cancer, is also effective in the treatment of other cancers (1, 3, 6, 8, 11). Therefore, studies have been done to determine the effect of flaxseed on ovarian cancer. The results of a study by Dikshit et al. (2017) showed that flaxseed supplementation resulted in the apoptosis of ovarian cells. Therefore, it reduced the tumor burden, and the severity and frequency of ovarian cancer among the laying hens (57). A study conducted by Dikshit et al. (2016) on 2.5-year-old hens who fed a diet containing 15% flaxseed, a fat-free diet of flaxseed, or flax oil 5% for 3 months. The results showed that flaxseed diet had a protective effect on the hens' ovary by altering the signal and metabolism of estrogen (58).

Delman et al. (2015) conducted a study on female rats, which received 0, 10, or 100 PPM of secoisolariciresinol diglucoside in their diet. The breast glands and epithelial ovarian tissue were examined after 3 months. The treatment with secoisolariciresinol diglucoside resulted in the normalization of dysplasia, the number of cells, and the expression of several genes which were affected by carcinogenesis. However, there was no evidence to suggest that secoisolariciresinol diglucoside improved the preneoplastic progression in the ovary (59). The study by Hales et al. (2014) on white laying hens showed that nutritional intervention by

flaxseed affected the pathways regulating morphogenesis and subsequently altering the progression of ovarian cancer (60).

In a study by Eilati et al. (2013), a standard diet enriched with flaxseed 10% was conducted on hens for 1 year. The results showed that the incidence and severity of ovarian cancer decreased among hens fed with diets containing flaxseed 10%. The results of this study could be the basis for nutritional interventions in clinical trials for the prevention and treatment of ovarian cancer among humans (61). Ansenberger et al. (2010) carried out a study on white laying hens fed with a diet enriched in flaxseed 10% for one year. The results showed a significant reduction in the severity of ovarian cancer; however, it did not reduce the prevalence of the disease. Flaxseed-fed hens had higher general health and fewer mortality rates. The results of this study could be the basis to carry out clinical trials among humans in order to evaluate the effect of flaxseed on ovarian cancer as a chemical suppressor (62). The results of studies which have been carried out on laying hens indicate the protective effect of flaxseed on ovarian cancer. Nevertheless, clinical trials should be conducted on humans in order to achieve more definite results.

Flaxseed and Sex hormones

The effect of flaxseed on the level of sex hormones has also been studied. In the study by Sturgeon et al. (2008), it was shown that flaxseed moderately reduced the level of sex hormones, especially among obese or overweight individuals (63). Two small interventional studies were conducted on 20 and less than 20 postmenopausal women. The participants were assigned into two groups of treatment with daily 25 g flaxseed for 16 weeks and 40 g flaxseed on a daily basis for 3 months. According to the results, no change was observed in serum levels of estradiol, Estrone sulfate, and sex hormone-binding globulins (64, 65).

In a cross-over trial conducted by Frische et al. (2003), 16 non-menopausal women were investigated for 4 periods and 2 menstrual cycles. In addition to their routine diet, the women during this period did not receive flaxseed or wheat flour. However, they either received 10 gr

flaxseed, or 28 gr wheat flour, or a combination of 10 gr flaxseed and 28 gr wheat flour per day. Blood samples were taken in the middle of the luteal phase and no changes were observed within the flaxseed group in terms of hormone levels (66). In a cross-over clinical trial conducted by Hutchins et al. (2001), 28 postmenopausal women were observed during three cycles of 7 weeks. The participants consumed 0, 5, or 10 gr flaxseed along with their usual diet. The blood samples were tested in the last week of each intervention period. According to the results, the flaxseed diet significantly reduced the amount of 17 beta-estradiol and estrone sulfate followed by an increase in prolactin levels. However, blood levels were not altered in terms of androstenedione, estrone, sex hormones binding globulins, progesterone, testosterone, free testosterone, dehydroepiandrosterone, and dehydroepiandrosterone sulfate with regard to the flaxseed diet (67).

A cross-sectional randomized study on 28 postmenopausal women showed that the use of flax supplementation as 5 to 10 gr per day for 21 weeks significantly decreased serum levels of estradiol and estrone sulfate. However, the levels of estrone, sex hormones binding globulins, and testosterone remained unchanged in this study (68). The results of the mentioned studies are not sufficient in order to obtain definitive conclusions regarding the effect of flaxseed on the level of blood hormones. Moreover, there are also controversies regarding the effectiveness of this substance on the levels of blood hormones. Therefore, further studies are needed to shed lights on the efficacy of this substance.

Side effects of flaxseed with regard to the performed studies

According to the available data, it seems that flaxseed is safe when administered orally and in recommended dosage for less than 4 months among healthy individuals. The long use of flaxseed is reported being accompanied by minor side effects (6). In the performed studies, the reported side effects include diarrhea (1, 3, 12, 16, 20, 48, 50), abdominal distension (1, 20), stomach pain (48), abdominal distension (1, 3, 5, 16, 20, 48), nausea (1, 12, 16), increased intestinal excretion (5), constipation (16), feeling of satiety (5), headache (20), and allergy

(20).The digestive complications of flaxseed are possibly due to the presence of high fiber, and the fluidity characteristic, and allergy to this

substance (1, 6). It has been reported that

Table 1. Characteristics of the investigated studies

Author/Year	Study type	Place of study	The purpose of the study	Number of samples	Number of studied group	Duration of use	Tool's of study	Result
Cetisli et al. (2015)	Clinical Trial	Turkey	Effect of flaxseed use on menopausal symptoms and quality of life	140 postmenopausal women	3 groups 1) 5 grams of flaxseed 2)Hormone Therapy (2mg of estradiol and 1 mg of Norethindrone Acetate) 3) control	12 weeks	A demographic questionnaire, menopause rating scale, short form of quality of life questionnaire	Significant reduction in hot flashes and increased quality of life
Pruthi et al. (2012)	Randomized, placebo control trial	United States of America	Evaluate the efficacy of flaxseed in reducing hot flashes	188 postmenopausal women with and without breast cancer	2 groups 1) 7/5 grams of flaxseed 2) Placebo	6 weeks	Hot flash related daily interference scale (HFDIS), the profile of mood states (POMS), the menopause quality of life scale (MenQOL), the global impression of benefit, and a side effect questionnaire	The same reduction in hot flashes in flaxseed and placebo groups
Colli et al. (2012)	Randomized, placebo control trial	Brazil	Effect of seed and flaxseed extracts on reducing menopausal symptoms	90 Postmenopausal women	3 groups: 1) Two capsules of 500 mg containing 1 gram of flaxseed extracts 2) 90 grams of flaxseed 3) Two capsules of 500 mg containing 1 gram of collagen	6 months	Kupperman Index	A non-significant reduction in hot flashes in the two groups of flaxseed and flax extract, compared to placebo
Turkestanti et al. (2012)	Double-blind randomized clinical trial	Iran	Comparison of the effect of flaxseed and soybean on menopausal hot flashes	90 postmenopausal women with hot flashes	3 groups: 1) 25 grams of flaxseed 2) 25 grams of soy 3) 25 grams of wheat flour	8 Weeks	A demographic questionnaire, checklist of intensity and duration of hot flashes	Reduction in the severity of hot flashes in both flaxseed and soybean groups and a decrease in the frequency of hot

Table 1. Continued								flashes in the soybean group
Turkestanti et al. (2011)	Randomized clinical trial	Iran	The Effect of fenugreek and flaxseed on menopausal hot flash	60 postmenopausal women with hot flashes	2 groups: 1) 6 grams of fenugreek 2) 25 grams of flaxseed powder	4 weeks	Demographic questionnaire, checklist of intensity and frequency of hot flashes	A non-significant reduction in the intensity and frequency of hot flashes in the two groups at the end of week 4, a significant reduction in the intensity of hot flash in the flaxseed group at the end of week 8.
Baghdari et al. (2011)	A double-blind randomized crossover study	Iran	Effect of 6-weeks consumption of flaxseed on vasomotor hot flashes in climacteric women	62 women aged at least 41 years with five moderate to severe hot flashes	2 groups: 1) 40 grams of flax seed 2) 40 grams of wheat flour	6 Weeks	Daily hot flashes and night sweats check list	6-week consumption of flaxseed powder may be effective in the reduction of vasomotor symptoms, especially for women with moderate vasomotor symptoms, compared to women with more and severe symptoms.
Simbalista et al. (2010)	Randomized clinical trial	Brazil	Daily Effects of flaxseed on menopausal symptoms	38 postmenopausal women	2 groups: 1) 25 grams of flaxseed 2) 25 grams of wheat bran	12 weeks	Kupperman Index	The non-significant reduction in the intensity of hot flash in the two groups
Pruthi et al. (2007)	Clinical trial	United States of America	Effect of flaxseed on menopause hot flashes	28 postmenopausal women with hot flashes	40 grams of flaxseed	6 weeks	Hot flashes daily registration form	Significant reduction in hot flashes in the flaxseed,

Table 1. Continued								
Lewis et al. (2006)	Double-blind randomized clinical trial	Canada	Effect of flaxseed on hot flashes and quality of life in postmenopausal women	99 postmenopausal women	3 groups 1) 25grams of flaxseed 2) 25 grams of soy 3) 25 grams of wheat flour	16 weeks	Daily record of hot flashes, quality of life questionnaire related to menopause	compared to the placebo group Non-significant effect of soybean and flaxseed on hot flashes and quality of life
Dodin et al. (2005)	Double-blind randomized clinical trial	Canada	The effect of flaxseed dietary supplement on lipid profile, bone mineral density, and symptoms in menopausal women	179 postmenopausal women	40 grams of flaxseed	12 months	Demographic questionnaire, frequency assessment questionnaire, quality of life questionnaire related to menopause	Not clinically significant effect on menopausal symptoms, bone mineral density, and lipid profiles
Lemay et al. (2002)	Randomized cross-over study	Canada	Effect of flaxseed and hormone therapy on menopausal symptoms and blood cholesterol	25 postmenopausal women	2 groups: 1) 40 mg of flaxseed per day 2) 0/625 mg of conjugated estrogen	2 months	Kupperman Index	Significant reduction in menopausal symptoms in both groups
Dalais et al. (1998)	A double-blind randomized cross-over study	Australia	Effect of phytoestrogens in postmenopausal women	52 postmenopausal women	3 groups: 1) 45 grams of flaxseed 2) 45 grams of soybean 3) 45 grams of wheat flour	12 weeks	Hot flashes daily registration form	Significant reduction in hot flashes in flax and placebo groups
McCann et al. (2014)	Factorial trial	New York	Effect of flaxseed and aromatase seed and their interaction on breast tumor	28 postmenopausal women with positive estrogen receptor tumor	4 groups: 1) 25 grams of flaxseed +1 placebo pills 2) 1 mg anastrozole 3) 25 grams of flaxseed + 1 mg of anastorsulin 4)1 Placebo Pill	13-16 days	Biopsy and mass resection	No significant effect of flaxseed on breast tumor
Lowcock et al. (2013)	Case-control	Canada	Relationship between consumption of flaxseed and lignin-	2999 women with breast cancer and 3370 healthy women	-	-	Food frequency questionnaire	A significant decrease in breast cancer

			containing foods on breast cancer					with 20-30 % flaxseed
Table 1. Continued								
Fabian et al. (2010)	Randomized clinical trial	United States of America	The effect of lignans on breast cancer in premenopausal women	45 non-menopausal women exposed to high risk of breast cancer	50 mg secoisolariciresinol diglucoside	12 months	Laboratory evaluation of biomarkers	Reducing cell proliferation by 25-50% and improving the histological characteristics of the tumor, however, short-term use of lignans does not have any effect on breast cancer.
Cotterchio et al. (2008)	Case-control	Canada	The effect of daily intake of phytoestrogens on the risk of breast cancer	3063 women with breast cancer and 3430 healthy women	-	-	Food frequency questionnaire	The use of lignans in non-postmenopausal women reduces the risk of breast cancer, and the body mass index affects the level of this risk.
Fink et al. (2017)	Case-control	New York	Intake of flavonoids and breast cancer risk	1837 cases and 1508 control	-	-	Food frequency questionnaire	Reduction in the risk of breast cancer in postmenopausal women with lignans

Thanos et al. (2006)	Case-control	Canada	Intake of phytoestrogens during adolescence and breast cancer risk	3024 cases and 3420 control	-	-	Food frequency questionnaire	The use of phytoestrogens in adolescence is associated with a reduction in the risk of breast cancer in adulthood
Table 1. Continued								
Thompson et al. (2005)	Double-blind randomized clinical trial	Canada	Effect of flaxseed use on biological tumor markers in postmenopausal women with Breast cancer	32 postmenopausal women with breast cancer	2 groups: 1) 25 grams of flaxseed 2) 25 grams of placebo	Between the first biopsy and surgery	Biopsy of breast mass	Reduction in cell proliferation and an increase in apoptosis by daily intake of 25 grams of flaxseed
McCann et al. (2004)	Case-control	New York	The relationship between dietary intake and the risk of breast cancer	1122 women with breast cancer and 2036 healthy women	-	-	Food frequency questionnaire	Reduction in the risk of breast cancer with the use of lignans in premenopausal women
McCann et al. (2002)	Case-control	New York	The relationship between lignin consumption and breast cancer risk	207 women with breast cancer and 188 healthy women	-	-	Food frequency questionnaire	Lignan's protective effect on breast cancer risk in non-postmenopausal women
Horn-Ross et al. (2002)	Case-control	United States of America	The effect of diet on the risk of breast cancer	1326 women with breast cancer and 1657 healthy women	-	-	Food frequency questionnaire	No association between phytoestrogens and the risk of breast cancer

Jafarnezhad et al. (2016)	Clinical trial	Iran	Effect of flaxseed, evening primrose oil and vitamin E on the severity of cyclic mastalgia	90 women with cyclic mastalgia	3 groups: 1) 30 grams of flaxseed 2) 2 capsules of 1000 mg evening primrose oil 3) 1 capsule of 400 IU Vitamin E	2 months	Visual analog scale	A significant decrease in pain in all three groups	
Jafarnezhad et al. (2017)	Semi-experimental clinical trial	Iran	The effect of flaxseed, evening primrose oil and vitamin E on the duration of periodic breast pain	90 women with periodic mastalgia	3 groups: 1) 30 grams of flaxseed 2) 2 capsules of 1000 mg Evening primrose Oil 3) 1 capsule of 400 IU Vitamin E	2 months	A form of the daily record of pain duration	Reduction in duration of periodic breast pain in the flaxseed group	
Table 1. Continued									
Mirghafourvand et al. (2016)	Randomized controlled trial	Iran	Effects of Vitex agnus and flaxseed on cyclic mastalgia	159 women with periodic mastalgia	3 groups: 1) 25 grams of flaxseed + placebo 2) Vitagnus tablet + flaxseed 3) Placebo tablets and placebo powder	2 months	Cradiff chart	Flaxseed and V. agnus are effective for a short-term period in decreasing cyclical mastalgia.	
Vaziri et al. (2014)	Clinical trial	Iran	Effect of flaxseed and omega-3 fatty acid supplement on cyclic mastalgia	181 women with cyclic mastalgia	3 groups: 1) 30 grams of flaxseed 2) omega-3 Fatty acids supplement 3) placebo	2 months	Visual analog scale	Reduction in cyclic mastalgia with flaxseed	
Goss et al. (2006)	Double-blind randomized clinical trial	United States of America	Effect of flaxseed on cyclic mastalgia	116 women with severe cyclic mastalgia	2 groups: 1) 25 grams of flaxseed 2) placebo	4 months	Visual analogue scale	Significant improvement in cyclic mastalgia	
Mirghafourvand et al. (2016)	Randomized controlled trial	Iran	Effects of vitex agnus and flaxseed on premenstrual syndrome	159 women with premenstrual syndrome	3 groups: 1) 25 grams of flaxseed + placebo 2) Vitagnus tablet + flaxseed 3) placebo tablets and placebo powder	2 months	assessment of premenstrual symptoms form	The effect of flaxseed and vitex agnus on improving premenstrual syndrome	
Dikshit et al. (2017)	Clinical Trial	United States of America	Effect of flaxseed on laying hens' ovarian cancer	235 laying hens	4 groups: 1) Flaxseed diet 2) Fat-free flaxseed diet 3) Flaxseed oil diet	11 months	Biopsy of ovarian and liver tissue	Reduction in the severity and frequency of ovarian cancer in	

Dikshit et al (2016)	Clinical Trial	United States of America	The effect of flaxseed and its components on the ovarian malignancies laying hens	120 laying hens	4)control 4 groups: 1)Full flaxseed 2)Fat-free flaxseed 3) Flaxseed oil 4) control	3 months	Ovarian biopsy	Protective effect of flaxseed diet on ovarian cancer in laying hens
Delman et al (2015)	Clinical Trial	United States of America	Effects of flaxseed lignan secoisolariciresinol diglucoside on preneoplastic biomarkers of cancer progression in a model of simultaneous breast and ovarian cancer development.	30 female rats	3 groups: 1) 0 2) 10 3) 100 PPM secoisolariciresinol diglucoside	3 months	Ovarian and breast biopsy	No effect of flaxseed on improvement in the ovarian pre-neoplastic status
Table 1. Continued								
Ansenberger et al (2010)	Clinical Trial	United States of America	Effect of flaxseed on the severity of ovarian cancer in laying hens	387 white laying hens	2 groups: 1)A diet containing 10 %flaxseed 2)Standard diet	12 months	Ovarian biopsy	Reduce severity but not the prevalence of ovarian cancer
Sturgeon et al (2008)	Clinical trial	United States of America	Effect of flaxseed on the level of sex hormones in patients with advanced breast cancer	48 postmenopausal women	In the first 6 weeks, 7/5 grams per day of flaxseed In the second 6 weeks, 15 grams per day of flaxseed	3 months	Laboratory measurement of sex hormones	Reducing the level of sex hormones, especially in obese or overweight people
Brooks et al (2004)	Clinical Trial	Toronto	The effect of flaxseed supplementation on estrogen metabolism in postmenopausal women	46 postmenopausal women	3 groups: 1) 25 grams of soy flour 2) 25 grams of flaxseed 3) Placebo	4 months	Laboratory measurements of blood and urine	No changes in serum levels of estradiol, estrone sulfate, or sex hormones binding globulins
Lucas et al (2002)	Double-blind randomized clinical trial	United States of America	Effect of flaxseed on the metabolism of lipids and bivariate biomarkers among postmenopausal women	58 postmenopausal women	2 groups 1) 40 grams of flaxseed 2) Placebo	3 months	Laboratory blood test	Improve lipid profile with flaxseed and no effect on sex hormones and bone biomarkers

Frische et al (2003)	Clinical trial	United States of America	Effect of flaxseed and wheat flour on serum hormones and lignan excretion in premenopausal women	16 premenopausal women	4 groups: 1) 10 grams of flaxseed 2) 28 grams of wheat flour 3) Combine cottonseed and wheat flour 4) Placebo	2 months	Laboratory blood test	No effect of flaxseed on blood hormones
Hutchinson et al (2001)	Crossover clinical trial	United States of America	Effect of flaxseed on Serum hormones in postmenopausal women	28 postmenopausal women	3 groups: 1) 0 2) 5 3) 10 gram flaxseed	21 weeks	Blood sample test	Significant reduction of 17 beta-estradiol and estrone sulfate in the flaxseed group
Table 1. Continued								
Haggans et al (1999)	Crossover clinical trial	United States of America	Effect of flaxseed on estrogen urinary metabolites in postmenopausal women	28 postmenopausal women	3 groups: 1) 0 2) 5 3) 10 grams of flaxseed	21 weeks	Urine sample test	Significant reduction of estradiol and estrone sulfate with flaxseed

intestinal obstruction may occur after the use of flaxseed resulting from its accumulation as a mass in the intestine, or the inadequate consumption of water and fluids. The use of flaxseed and its oil is not recommended during pregnancy and lactation. Animal studies have shown poor results and human data are inadequate in this domain. Flaxseed can stimulate menstruation and produce hormonal effects that can be harmful to pregnancy (6).

Discussion

In general, in most studies, flaxseed was effective in reducing the symptoms of menopause and hot flashes. However, the results of some studies are significant due to different sample size, the different dosage of flaxseed, the frequency of consumption and, the duration of use. Moreover, with regard to the results of most of these studies, the use of flaxseed during menopause can be suggested reduce the symptoms of hot flashes. The positive effect of flaxseed on hot flashes is possibly caused by phytoestrogens that are accompanied

with an increase in estrogen levels and changes in hormonal balance, thereby reducing the frequency of other vasomotor symptoms (1, 7).

More clinical trials are needed regarding the effect of flaxseed on breast cancer; however, overall evidence suggests that flaxseed and its components play an important role in reducing the risk of breast cancer and its treatment. Furthermore, its use among patients with breast cancer is reported being safe (11). Most studies have shown positive effects of flaxseed on reducing the risk of breast cancer, especially among postmenopausal women.

Nevertheless, more research is needed in order to obtain more definite results. This effect may be due to the fact that lignans can affect the risk of breast cancer by modulating the endogenous estrogen metabolism or competing for inhibition with estrogen receptors (9). This results from the presence of estrogen and lignin that inhibit the growth of cells in the type of estrogen-dependent breast cancer (8). The results of all studies on the use of flaxseed on cyclic mastalgia indicate a positive effect of this

plant on cyclic mastalgia. Therefore, this drug can be used for this purpose.

Due to the presence of substances in flaxseed and fewer side effects of herbal drugs, compared to chemical drugs, women prefer to use complementary medicines. Therefore, flaxseed can be used safely in the treatment of premenstrual syndrome (50). However, more studies and a longer intervention period are needed in order to better understand its effectiveness. The effect of flaxseed on the improvement of cyclic mastalgia can be explained by the high levels of lignans phytoestrogens. In addition, this plant inhibits the activity of the aromatase enzyme, thereby reducing the production of estrogen (3). On the other hand, the lignan chemical structure is similar to estradiol and estrogen receptor selective modulators, such as tamoxifen, that are used to treat mastalgia (8). There is only one study regarding the positive effect of flaxseed on the premenstrual syndrome. With this background in mind, several studies should be performed in this regard to obtain more clear results. The effect of flaxseed on the symptoms of this syndrome is probably due to the fact that flaxseed is a rich source of phytoestrogens (48). Phytoestrogens-enriched sources are effective in the alleviation of the symptoms of premenstrual syndrome (56).

The effectiveness of flaxseed on the prevention and treatment of ovarian cancer due to its anti-cancer effect has also been studied (52). Ovarian cancer is the most fatal gynecologic malignancy; therefore, the prevention of this cancer is the best approach to reduce the tumor cell growth. The presence of omega-3 fatty acids in this plan can be effective in the prevention of this cancer (69). The results of animal studies indicate a reduction in the severity of this cancer; however, human studies are recommended in this regard. The effect of flaxseed on sex hormone levels is still questionable due to the limited number of studies and small sample sizes; therefore, it necessitates further research in this regard.

Conclusion

According to the results, it can be concluded that flaxseed has a positive effect on the improvement of symptoms of menopause and hot flashes. Moreover, it reduces the risk of

breast cancer and improves cyclic mastalgia and premenstrual syndrome. The efficacy of this plant on the reduction of this cancer among animal samples was observed; however, further studies are needed on the evaluation of the effect of flaxseed on cancer treatment among humans. With regard to the ovarian cancer treatment, the efficacy of flaxseed has been observed among animal samples; however, more research is needed to be conducted on human samples in this domain. On the other hand, the obtained results from the effect of this plant on the sex hormone levels are not definite. This paves the way for further studies on the relation between flaxseed and hormone levels. With respect to the other beneficial properties of flaxseed and minor side effects, the use of this plant can be regarded at Obstetrics and Gynecology among various cases which have been mentioned.

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Conflicts of interest

The authors declare no conflicts of interest.

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