



Effectiveness of Herbal Medicines Containing Phytoestrogens to Treat Cyclic Mastalgia: A Systematic Review and Meta-Analysis

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Abstract

Background: Despite the high prevalence of cyclic mastalgia (cyclic breast pain), and disagreement about its therapeutic methods, there is a lot of ambiguity about breast pain yet. We aimed to assess the effectiveness of phytoestrogens to treat cyclic mastalgia, based on the available evidences.

Materials and Methods: In this systematic review and meta-analysis, systemic search of online databases (Scopus, Cochrane Central Register of Controlled Trials, EMBASE-Ovid, and Medline complete) for randomized control trial and non-randomized prospective or retrospective clinical studies published up to August 2021 that use oral appliances for the treatment of cyclic mastalgia in women was conducted. Study selection was done by two reviewers.

Results: Totally, eight studies were included. Results of the meta-analysis showed that Isoflavones, Nigella sativa, Cinnamon Chamomile tea, Vitagnus and Flax seeds, reduce mastalgia pain; also phytoestrogens (SMD:-1.40; 95%CI: -1.93 to -0.89), and its sub-groups such as Flaxseed (SMD:-1.48; 95% CI: -2.46 to -0.512), and Vitex agnus-castus (SMD:-1.78; 95%CI: -2.88 to -0.68; p<0.001) were found significantly effective on the severity of cyclic mastalgia. However, heterogeneity index of all studies was at a significantly high level and was estimated in the range of moderate to high. Also, Nigella sativa, Chamomile, Red clover, and Cinnamon significantly reduced the severity of cyclic mastalgia.

Conclusion: Phytoestrogens may have effective and helpful effects on improving cyclic breast mastalgia. Findings of the present study should be interpreted carefully because of existing high heterogeneity between studies, few numbers of studies and small sample size.

Key Words: Cyclic breast pain, Herbal Medicine, Cyclic mastalgia, Phytoestrogens.

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1- INTRODUCTION

Mastalgia or breast pain is one of the most common complaints that women refer to the doctors for. Mastalgia is a medical term used for a painful breast, clinically, with two categories of cyclical and non-cyclical breast pain. The cyclical mastalgia refers to moderate to severe breast pain that lasts for ≥ 5 days, and usually occurs between the ages of 20 and 30 years and even in the postmenopausal period (1). Although the prevalence of mastalgia varies in different communities, about 41 to 69% of women experience cyclical mastalgia. The duration of mastalgia is more than 5 days per cycle in 25 to 30% of patients (2). No obvious cause for this pain has been identified so far. One of these reasons may be attributed to inflammatory cytokines. A study showed the presence of tumor necrosis factor- α (TNF- α), and interleukin in patients with mastalgia. According to previous reports, cytokine levels in patients are lower during the luteal phase, but not statistically significant. Other possible etiologies of mastalgia include decreased progesterone, increased estrogen, and estrogen/progesterone imbalance (3).

Although the cause of cyclical mastalgia is not yet known, hormonal stimulation may be one of the possible reasons due to the onset of the condition in the luteal phase. It has been reported that possible causes of this disorder can be attributed to high estrogen levels, low progesterone levels and estrogen/progesterone ratio imbalances (4). The majority of women (75 to 85%) generally do not need treatment (5), and the rest of the women experience constant pain that interferes with daily activities, which means that they need treatment (5).

Mastalgia can be alleviated with the help of various treatments, such as the administration of vitamin B6, B2, C and E, non-steroidal inflammatory drugs

(NSAIDs), thyroxin, diuretics, progestational agents, Bromocriptine, Centchroman, Tamoxifen, Danazol, Vitexagnus castus plant extract, and Evening primrose oil (7-9). Complications of hormone therapy have led women to use herbal remedies (6). Accordingly, much attention has been paid to herbal and complementary therapies in the treatment of cyclical mastalgia, as in numerous health issues (4). Medicinal plants have unique properties compared to chemical drugs, including cost-effectiveness and fewer side effects (7). Phytoestrogens have some compounds similar to 17- β -Sterol in structure and function, or may have some effects similar to estrogens. Phytoestrogens include Lignans, Isoflavonoids and coumestans (8).

Based on our knowledge, no meta-analysis has assessed the effectiveness of phytoestrogens on cyclic mastalgia; so the purpose of the present study was to assess the effectiveness of phytoestrogens to treat cyclic mastalgia, based on the available evidences.

2- MATERIALS AND METHODS

Preferred Reporting Items for Systematic review and Meta-Analysis (PRISMA) checklist was used as a template for this review.

2-1. Participants: Women up to 45 years old.

2-2. Outcome: Reduction of cyclic mastalgia.

2-3. Included studies: Randomized controlled trials (RCT), clinical studies both randomized and nonrandomized, either retrospective or prospective. Due to the limited number of published RCT in the literature other types of clinical studies were included. Pilot, preliminary and case report studies were not included due to limited sample size and higher risk of bias. Studies published in English up to August 2021.

2-4. Information sources

Systemic research of electronic databases: systemic search of online databases (Scopus, Cochrane Central Register of Controlled Trials, EMBASE-Ovid, and Medline complete), for randomized control trial and non-randomized prospective or retrospective clinical studies published up to August 2021.

2-5. Search

The search was undertaken by two separate reviewers to investigate the effects of phytoestrogens on cyclic mastalgia, using keywords such as (Mastalgia OR Breast pain OR Chest pain) AND (Complementary treatments OR Alternative treatments OR Phytoestrogens OR Herbal medicine OR Alternative medicine OR Complementary medicine OR Complementary therapies OR Vitex).

2-6. Study selection

Database search was done for possible studies, abstracts of the studies were screened for identification of eligible studies, full text articles were obtained and assessed and a final list of included studies was made. This process was done independently and in duplication by two reviewers and any disagreement was resolved by the 3rd reviewer.

2-7. Data collection process

We developed a researcher made form and followed it for each study. Two reviewers collected the data, independently collected data was combined and compared for accuracy any discrepancies were solved by a third reviewer.

2-8. Data items

A pre-designed checklist was used independently by two authors to extract relevant data such as authors, year of publication, age of patients, place of study (country), type of intervention, percentage of dropouts, instrument of study, number

of subjects in case and control groups, and main outcomes (**Table.1**).

2-9. Risk of bias in individual studies

The quality of articles was assessed based on the Jadad scale (9), which consists of three main domains of randomization (method of randomization and appropriateness of randomization), blinding (method of blinding and suitability of blinding) and dropouts or withdrawals. The Jadad scale is scored on a scale of 0 to 1. The items were assessed by two researchers independently and any disagreement was resolved by a third party (**Table.2**). In addition, intention to treat and baseline comparability were included in the Jadad scale.

2-10. Data analysis

The software Comprehensive Meta-Analysis Version 2.0 (CMA 2.0) was used in order to do data analysis. Finally, the heterogeneity index of studies was determined by Q Cochran test and I2 index and a p-value of less than 0.1 was considered significant (indicating presence of heterogeneity). The I2 index assessed whether the variance across studies was real or not due to sampling errors. According to the results of Higgins et al. (7), it is considered that values lower than 25 percent show low heterogeneity, values in the range of 25-75 percent show moderate heterogeneity and values more than 75 percent show high levels of heterogeneity. According to the results of heterogeneity, random was used to report the effect of phytoestrogens if heterogeneity was 25 percent or higher instead of fixed effect. Forest plot was used in order to demonstrate the results of meta-analysis, the size of square shows the number of samples of each study and drawn lines on both sides show 95 percent confidence interval (CI) for the effects of each study. Additionally, publication bias was assessed by a Funnel plot and Egger's and Begg's tests (10).

3- RESULTS

Characteristics of 8 studies included in our systematic review and meta-analysis are shown in **Table.1**. In **Figure.1**, the

process of selecting these 8 studies in the systematic review has been shown. Quality assessment of 8 studies is shown in **Table.2**.

Table-1: General characteristics of included studies.

Authors, Year, Country, (Reference)	Age/year	Number of subjects in intervention /control	Type of intervention		Time	Drop out (%)	Assessment tool	Results
			Case group	Control group				
Ingram et al, 2003, Australia, (11)	40± 6	Six women were randomized to placebo, five to the 40 mg/ day dose and seven to the 80 mg/day dose	Each tablet containing 40 mg of isoflavones was extracted from red clover, in addition to antioxidants	The placebo contained the same antioxidants, excipient and coating but no isoflavones	3 months	78.3	VAS	The reduction in pain was 13% for placebo, 44% for 40 mg of isoflavones per day and 31% for 80 mg per day.
Mirghafourvand et al., 2016, Iran, (12)	18–45	Flaxseed, n=53, Vitex agnus, n=53, and placebo group, n = 53	25 g of Flaxseed powder daily for two months, 2-3 g mg of V.agnus tablet daily, for two months	Placebo	2 months	0%	Cardiff breast pain chart	The results showed a significant reduction in both the severity and duration of breast pain in both intervention cycles.
Mirmolaei et al., 2016, Iran, (13)	15-49	Vitagnus syrup=36, and placebo syrup=36	Vitex-agnus-castus (8 ml) mixed with water and honey, daily for three months	10 ml syrup containing (oral paraffin, honey and water) for three months	5 months	6.9	VAS and Short Form Questionnaire McGill	Vitagnus in women who use bras and have a good nutrition with moderate to severe breast pain, certainly relieves pain.
Mirmolaei et al., Iran, 2017, (14)	15-49	Nigella Sativa=36, and placebo group=36	10 ml Nigella Sativa syrup containing (5ml Nigella Sativa, honey and water) for three months	10 ml syrup containing (oral paraffin, honey and water) for three months	5 months	9.7	VAS and Short Form Questionnaire McGill	Nigella Sativa reduces pain more than placebo.
Rajaby Gharaiy Iran 2017, (15)	Cinnamon= 26.2± 5.58 control group: 25.76± 4.65	Cinnamon group, n=37 and control group, n= 37	Capsules contained 400 mg of cinnamon (three capsules per day on all days of the patient's cycle during two months)	Placebo	2 months	0%	Cardiff breast pain chart	The mean scores of cyclical breast pain severity were significantly less in Cinnamon group than control.
Saghafi et al., Iran, 2017, (16)	Intervention= 26 ± 7.2 placebo group= 29 ± 6.8	Chamomile, n=30, and placebo group, n=30	Chamomile (15 drops) daily for two months	Placebo drops (distilled water)	2 months	0%	VAS and assessment of the breast pain chart (BPC)	Chamomile was a well-tolerated, secure and effective drug for

								treating women with mild to moderate mastalgia.
Vaziri et al., Iran, 2014, (4)	29.63± 7.05	61, 60, and 60 women, respectively, received flaxseed as bread, omega-3 fatty acids as pearl, and wheat bread, as their diet	Intervention group received flaxseed as bread (containing 40 g wheat flour), omega-3 fatty acids as pearl (contained 180 mg eicosapentaenoic acid, and 120 mg docosahexenoic acid), and wheat bread (containing 40 g wheat flour) as their diet	-	2 months	9.04	VAS	Flaxseed bread diet was an effective approach in decreasing cyclical mastalgia.
Sekhavat et al., 2009, Iran, (17)	Intervention= 30.2± 12.1, control group= 29±9+11.7	Vitex agnus-castus group=55, control group=62	60 drops containing 3.5 mg of Vitex agnus-castus	Placebo	3 months	2.5	VAS	Pain significantly decreased in Vitex agnus-castus than placebo.
VAS: Visual analogue scale.								

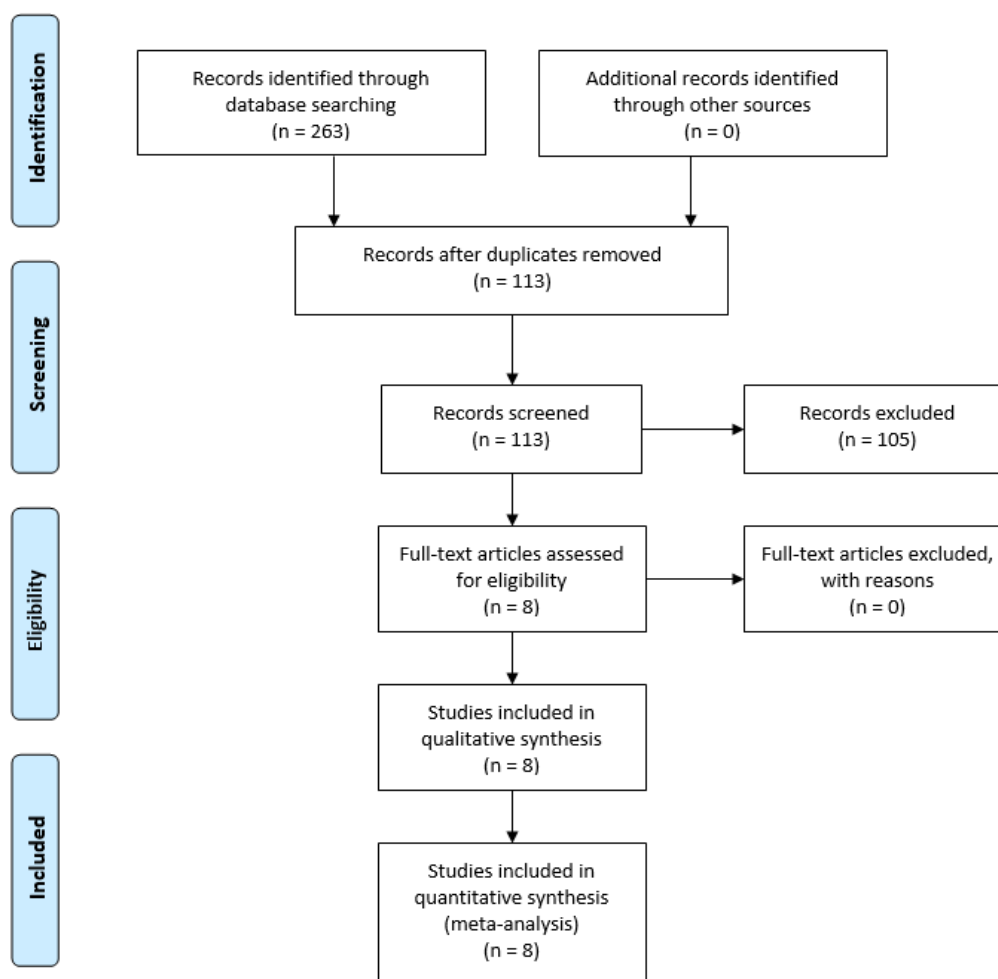


Fig.1: PRISMA flowchart.

Table-2: Assessment of quality of studies using Jadad scale (9).

Author, Year, (Reference)	Randomization			Blinding			Sample Account of all patients
	Mention Randomization	Method: Appropriate	Method: Inappropriate	Concealment Mention blinding	Method: Appropriate	Method: Inappropriate	
Ingram et al., 2003, (11)	*		*	*	*		*
Mirghafourvand et al., 2016, (12)	*	*		*	*		*
Mirmolaei et al., 2016, (13)	*	*		*	*		*
Mirmolaei et al., 2017, (14)	*		*	*	*		*
Rajaby Gharaiy et al., 2017, (15)	*	*		*	*		*
Saghafi et al., 2017, (16)							
Vaziri et al., 2014, (4)	*		*	-			*
Sekhavat et al., 2009, (17)	*	*		*			*

This study as a meta-analysis was carried out with ten plants on the results of eight studies. The results of Q Cochran test demonstrate the heterogeneity between the results of different studies and random model was used instead of fixed model of meta-analysis. The standardized mean

difference value between intervention and control group was (SMD-1.40; 95% CI: -1.93 to -0.88), and it is statistically significant (p<0.001), it also shows the phytoestrogen effects on the cyclic mastalgia (**Figure.3**).

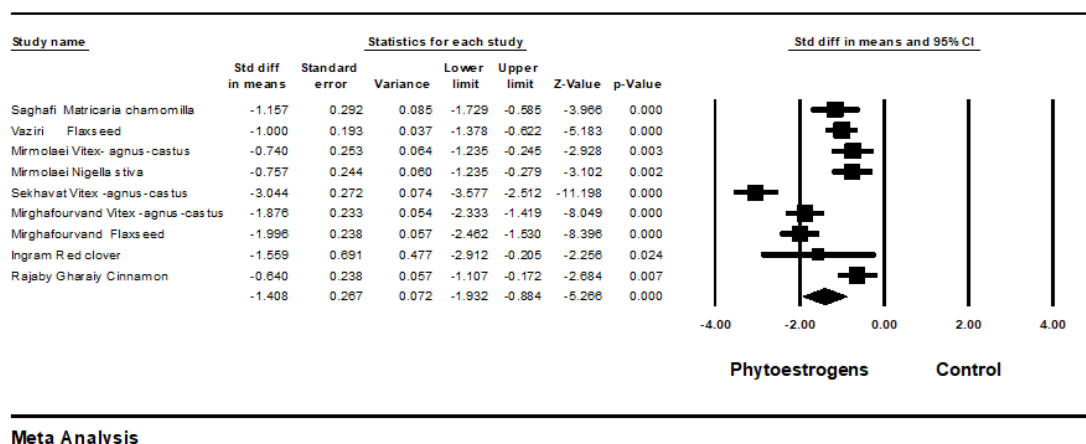


Fig.3: Effects of phytoestrigens on cyclic mastalgia. The horizontal lines denote the 95% CI; ■, Point estimate (size of the square corresponds to its weight); ♦, Combined overall effect of treatment.

Sensitivity analysis was conducted due to high heterogeneity ($p < 0.001$; $I^2 = 89.3\%$) between studies and the effect of each study on the final result was evaluated separately. None of studies had a significant effect on the final result and heterogeneity of study; also, sensitivity analysis was done according to the type of

treatment (Flaxseed and Vitagnus). The results of analyzing Flaxseed with two studies [Mirghafourvand et al. 2016 (12); Vaziri et al. 2014 (4)] showed that women in Flaxseed group reported significantly less pain than control group SMD: -1.48 (95% CI: -2.46 to -0.512) (Figure.4).

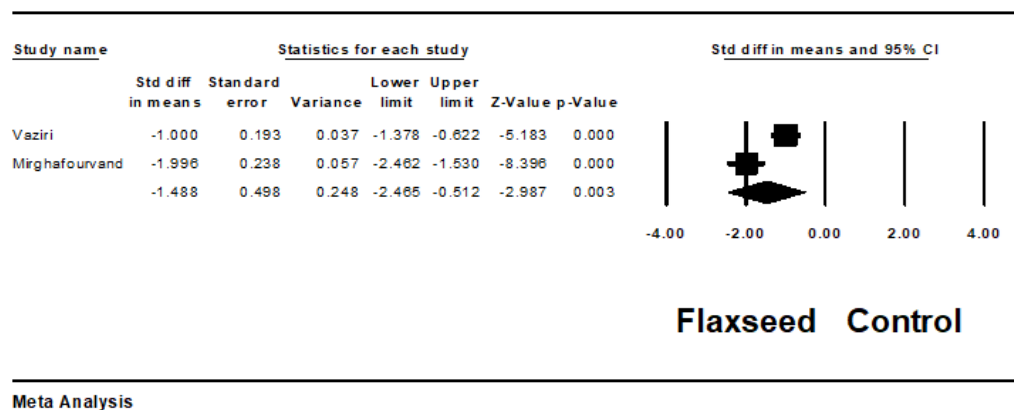


Fig.4: Effects of Flaxseed on cyclic mastalgia. The horizontal lines denote the 95% CI; ■, Point estimate (size of the square corresponds to its weight); ◆, Combined overall effect of treatment.

According to the value of heterogeneity index ($p < 0.001$; $I^2 = 90.56$), it is found that there is high heterogeneity between studies. But sensitivity analysis was unable to detect heterogeneity resource. The results of Vitex agnus-castus analysis with three studies [Mirghafourvand et al. 2016

(12); Mirmolaei et al. 2016 (13); Sekhavat and Zare Tarzejani 2009 (17)] showed that severity of pain was less in Vitagnus group compared to control, SMD: -1.78 (95% CI: -2.88 to -0.68 ; $p < 0.001$) (Figure.5).

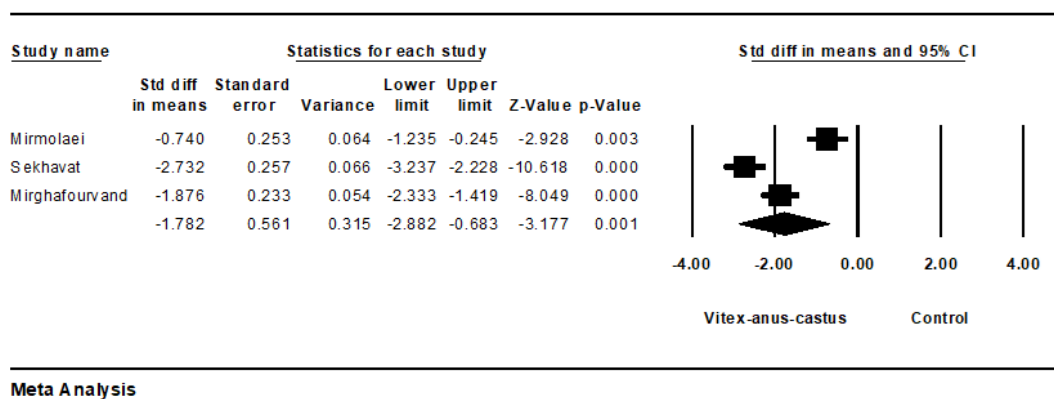


Fig.5: Effects of Vitex agnus-castus on cyclic mastalgia. The horizontal lines denote the 95% CI, ■, Point estimate (size of the square corresponds to its weight); ◆, Combined overall effect of treatment.

According to the values of heterogeneity index ($p < 0.001$; $I^2 = 93.51$), it is found that there is high heterogeneity between studies. Sensitivity analysis was done due to detection of potential resource; high heterogeneity of studies and the effect of all studies on final result and degree of

heterogeneity were separately evaluated. None of the studies had significant effect on the final result and degree of heterogeneity. Egger's test (intercept: -1.92 , $p = 0.89$), and Begg's test ($p = 0.630$) were not significant; funnel plot is drawn in **Figure.6**.

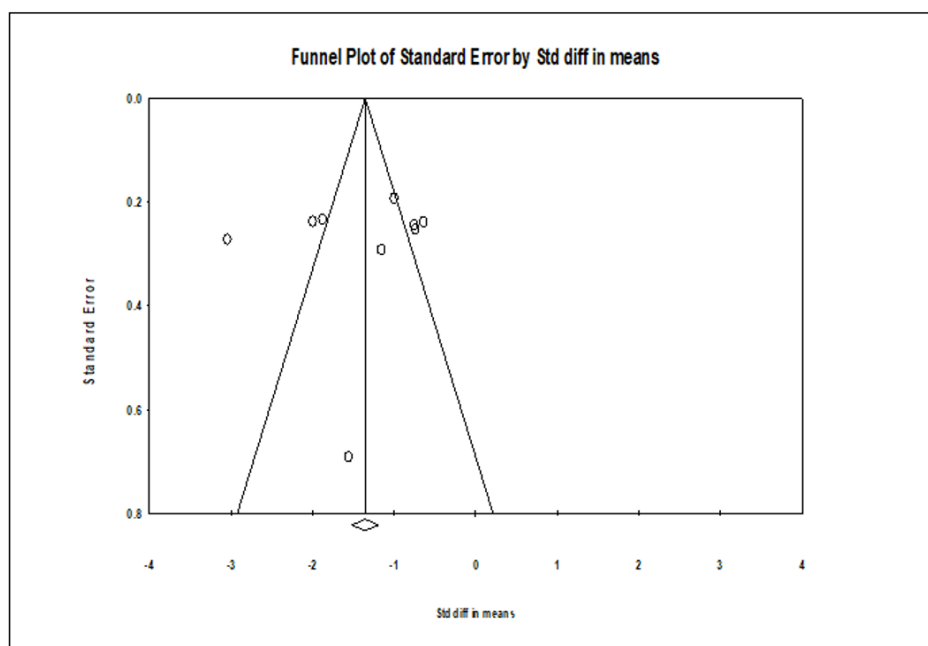


Fig.6: Funnel plot of published trials on the effects of phytoestrogens on mastalgia.

4- DISCUSSION

The results of the meta-analysis showed that phytoestrogens (SMD: -1.40 ; 95% CI: -1.93 to -0.89), and its sub-groups such as flaxseed (SMD: -1.48 ; 95% CI: -2.46 to -0.512), and Vitex-agnus-castus (SMD: -1.78 ; 95% CI: -2.88 to -0.68 ; $p < 0.001$) showed that they are significantly effective on the severity of cyclic mastalgia. However, heterogeneity index of all studies was at a significantly high level and was estimated to be in the moderate to high range. Also, *Nigella sativa*, Chamomile, Red clover, and Cinnamon significantly reduced the severity of cyclic breast mastalgia. Phytoestrogens may have effective and helpful effects on improving cyclic breast mastalgia; however, findings of the present study should be interpreted carefully

because of existing high heterogeneity between studies, few numbers of studies and small sample size. *Linum usitatissimum* (Linn.), commonly known as flaxseed or linseed, contains large amounts of plant lignans belonging to the branches of phytoestrogen, which have antioxidant properties (1, 2, 4, 17). Flaxseed also contains polyunsaturated fatty acids which can help better synthesize omega-3 fatty acids (1, 17). It inhibits aromatase activity and thus reduces estrogen production. The basic structure of phytoestrogen is similar to that of estradiol and selective estrogen receptor modulators (SERMs), including tamoxifen that is used to treat mastalgia (4, 18). One of the best studies on the effect of flaxseed on cyclical mastalgia is the study of Goss et al., whose findings are in good agreement with the present study.

According to their findings, the flaxseed has been suggested as the first line of treatment for mastalgia (19). Since flaxseed is affordable, tolerable and available (4), it can be prescribed to most target groups with different physical and economic conditions. Due to fewer side effects of flaxseed than chemical drugs, women can safely treat mastalgia during premenstrual syndrome (20). Flaxseed can also act as a protective factor against breast cancer in women (21). Therefore, studies suggest 25g daily flaxseed in premenopausal women (22). In a randomized controlled trial on 159 women with cyclical mastalgia, the results showed a significant improvement in breast pain in both intervention groups in the first and second months after the intervention. The mean score of patients who received 25g daily Flaxseed powder was significantly lower in the first month after the intervention compared to the group who received 3.2–4.8 mg daily vitagnus tablet (22). However, in a study by Jaafarnejad et al., the results showed that flaxseed, vitamin E, and evening primrose oil showed no difference in terms of mastalgia treatment (23). However, Vaziri et al. (2014) reported that the use of flaxseed was more effective in controlling mastalgia than omega-3 (4). Vitexagnus is an herbal medicine native to the Mediterranean region (24), which has an anti-prolactin activity and is effective in premenstrual syndrome and hypermenorrhea, and can be an alternative to complicated treatments such as danazol (25). In a randomized, placebo-controlled double-blind trial, the effect of a solution containing Vitex agnus castus (VACS) extract was investigated in patients with cyclical mastalgia. After one/two courses of treatment, the difference in the rate of pain relief by VACS was significantly greater than placebo (26). In another clinical trial, 60 drops of Vitexagnus were given for three months to women of menstruating age who complained of

breast pain. At the end of the treatment period, the results showed that about 88.4% of patients responded well to Vitexagnus and this drug was well tolerated in individuals and had no drug side effects (25). A review study on the effect of herbal medicines and dietary supplements on mastalgia found that Vitexagnus and Vitamin E had more evidence for use in the treatment of mastalgia (18). Herbal remedies have also become a common treatment and prevention method for mastalgia (27). Chamomile, cinnamon and red clover are known worldwide as phytoestrogenic plants. These plants also have an effective improvement in reducing mastalgia (1). In a study to determine the effectiveness of chamomile in controlling cyclical mastalgia, the results showed that administering chamomile for two months three times a day and five drops each time could be a tolerable, safe and effective drug for the treatment of women with mild to moderate mastalgia (6). Other trials have also reported the effect of cinnamon on reducing mastalgia (3). In the study of Mirmolaei et al., the research units were 72 women with cyclical mastalgia referred to the Center for Breast Cancer at Jihad of Tehran University in 2014-2015, who were randomly divided into intervention (Fennel flower syrup = 36), and placebo (Paraffin oil syrup = 36) groups. The pain intensity was measured two months before and three months after the intervention with visual analogue scale (VAS), and short-form McGill pain questionnaire (SF-MPQ). Thus, there was no significant difference between the fennel flower and placebo groups based on SF-MPQ, but there was a significant difference between the two groups based on VAS ($p=0.002$). According to the results, fennel flower alleviated the pain intensity more than placebo, so it can be prescribed along with other drugs to treat cyclical mastalgia (28). One of the main ingredients of fennel flower is thymoquinone, which may have

anti-inflammatory, anti-oxidant, anti-oxidative stress and anti-cancer properties. The chemical composition of fennel flower essential oil contains 17% saturated fatty acid and 82.5% unsaturated fatty acid. Linoleic acids (55.6%), oleic acid (23.4%), and palmitic acid (12.5%) are its main components. Scientific articles reported immune system boosting, antioxidant, anti-inflammatory and antihistamine properties in various compounds in fennel flower oil and hydroalcoholic extract. Other studies have suggested antimicrobial, gastrointestinal disorders-healing, blood pressure-lowering, blood glucose-lowering, blood lipid-lowering and anti-cancer properties, as well as protective properties for liver, kidney, nervous system, cardiovascular systems for this plant. In addition, this plant consumed in traditional medicine dosage has had no side effects (28). The analgesic properties of fennel flower have been proven in Ghamdi-Al's study in rats (29). The effectiveness of fennel flower in improving mastalgia has been confirmed in line with animal studies.

4-1. Study limitations

The first limitation of the study was the poor methodological quality of some of the articles included in this study. These shortcomings included the lack or inadequate reporting of random allocation sequences as well as blinding, suggesting that future studies should be designed and reported on a consort basis. Other limitations of this study were the small number of studies and their small sample size, which indicates the need for further research with a larger sample size in this field.

5- CONCLUSION

According to the results, Isoflavones, *Nigella sativa*, Cinnamon Chamomile tea, Vitagnus and Flax seeds, reduce pain more than placebo. Therefore, it can be used along with other medications for the

treatment of mastalgia. Phytoestrogens may have effective and helpful effects on improving cyclic breast mastalgia. Findings of the present study should be interpreted carefully because of existing high heterogeneity between studies, few numbers of studies and small sample size.

6- CONFLICT OF INTEREST: None.

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