http:// health-providers.ir
Systematic Review (Pages: 39-50)

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

Parsila Taheri[1], Masumeh Ghazanfarpour[2], Saeed Soleimany[3], Hosna Faridi[4], Samaneh Movahedinia[5], *Benyamin Fazli [6]

[1]Obstetrics and Gynecology Specialist, Infertility Fellowship, Mashhad University of Medical Sciences, Mashhad, Iran. [2]Student Research Committee, Kerman University of Medical Sciences, Kerman, Iran. [3]Regional Educational Blood Transfusion Center, Kerman, Iran. [4]Department of Nursing and Midwifery, Sanandaj Branch, Islamic Azad University, Sanandaj, Iran. [5]Kerman University of Medical Sciences, Kerman, Iran. [6]Assistant Professor of Intensive Care Medicine, Department of Anesthesiology, Mashhad University of Medical Sciences, Mashhad, Iran.

Abstract

Background: While cyclic mastalgia is a prevalent condition with varied treatment approaches, the effectiveness of phytoestrogens remains unclear. This systematic review aims to address this gap by evaluating the effectiveness of phytoestrogens in alleviating cyclic mastalgia based on the available evidence.

Materials and Methods: This systematic review and meta-analysis involved a comprehensive search of online databases (Scopus, Cochrane Central Register of Controlled Trials, EMBASE-Ovid, and Medline Complete) to identify randomized controlled trials and non-randomized prospective or retrospective clinical studies published up to August 2021. The search focused on studies evaluating the use of oral phytoestrogens for the treatment of cyclic mastalgia in women. Study selection was performed independently by two reviewers.

Results: This meta-analysis included eight studies. The results indicated that several interventions, including isoflavones, Nigella sativa, cinnamon chamomile tea, Vitex agnus-castus, and flax seeds, were associated with reduced mastalgia pain. Specifically, phytoestrogens (SMD: -1.40; 95% CI: -1.93 to -0.89), 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; $p < 0.001$) demonstrated significant effectiveness in reducing the severity of cyclic mastalgia. However, the heterogeneity across all studies was high, ranging from moderate to substantial. Further, Nigella sativa, chamomile, red clover, and cinnamon were also found to significantly reduce the severity of cyclic mastalgia.

Conclusion: While phytoestrogens like Isoflavones, Nigella sativa, Cinnamon Chamomile tea, Vitagnus, and Flax seeds show promise for relieving cyclic mastalgia, with Flaxseed and Vitex agnus-castus standing out, the evidence remains inconclusive due to variations and limitations in existing studies, highlighting the need for more research to confirm these benefits and guide optimal use.

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

*Please cite this article as: Taheri P, Ghazanfarpour M, Soleimany S, Faridi H, Movahedinia S, Fazli B. Effectiveness of Herbal Medicines Containing Phytoestrogens to Treat Cyclic Mastalgia: A Systematic Review and Meta-Analysis. Health Provid 2021; 1(1): 39-50. doi: **10.22034/HP.2022.146668**

Corresponding Author:

Benyamin Fazli, MD, Department of Anesthesiology, Mashhad University of Medical Sciences, Mashhad, Iran.

Email: Benjamin.fazli@yahoo.com

Received date: Aug. 10, 2021; Accepted date: Dec.22, 2021

1- INTRODUCTION

Mastalgia, or breast pain, is a frequent complaint among women seeking medical consultation. Clinically, mastalgia is categorized into cyclical and non-cyclical breast pain. Cyclical mastalgia, characterized by moderate to severe breast pain lasting ≥5 days, typically occurs in women between 20 and 30 years of age, and can persist into the postmenopausal period (1). While the reported prevalence of mastalgia varies across populations, approximately 41% to 69% of women experience cyclical mastalgia. In 25% to 30% of patients, this pain lasts for more than 5 days per menstrual cycle (2).

The underlying cause of cyclical mastalgia remains unclear, although inflammatory cytokines may play a role. Studies have detected tumor necrosis factor-α (TNF-α) and interleukins in patients with mastalgia. Some reports suggest lower cytokine levels during the luteal phase in these patients, although this difference is not always statistically significant. Other potential etiologies include decreased progesterone, increased estrogen, and estrogen/progesterone imbalance (3).

While the precise etiology of cyclical mastalgia remains unclear, hormonal fluctuations, particularly during the luteal phase, are suspected to play a role. Imbalances in estrogen and progesterone levels, including elevated estrogen, reduced progesterone, or an altered estrogen/progesterone ratio, have also been implicated (4). Although most women (75% to 85%) with cyclical mastalgia do not require medical intervention (5), the remaining patients experience persistent pain that interferes with daily activities, necessitating treatment.

Various treatments can alleviate mastalgia, including vitamin B6, B2, C, and E supplementation, non-steroidal anti-inflammatory drugs (NSAIDs), thyroxine, diuretics, progestational agents, bromocriptine, centchroman, tamoxifen, danazol, Vitex agnus-castus plant extract, and evening primrose oil (6-9). However, concerns regarding the complications associated with hormone therapy have led many women to explore herbal remedies (6). Consequently, there has been increasing interest in herbal and complementary therapies for cyclical mastalgia, mirroring trends observed in the management of numerous other health conditions (4). Compared to conventional pharmaceuticals, medicinal plants offer potential advantages, including cost-effectiveness and a reduced risk of adverse effects (7). Phytoestrogens, which include lignans, isoflavonoids, and coumestans (8), possess compounds structurally and functionally similar to 17-β-estradiol or exhibit estrogen-like effects. To our knowledge, no meta-analysis has specifically evaluated the effectiveness of phytoestrogens for treating cyclical mastalgia. Therefore, the purpose of this study was to assess the efficacy of phytoestrogens in alleviating cyclical mastalgia, based on the available evidence.

2- MATERIALS AND METHODS

This review followed the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines.

2-1. Eligibility criteria

The eligibility criteria were guided by the PICO (Participants, Interventions, Comparison, and Outcomes) framework, with particular emphasis on Participants and Outcomes due to the descriptive nature of the research.

- P (Participants): Women aged 45 years or younger.
- I (Interventions): Over-the-counter pain relievers, hormonal therapies, supplements (e.g., Evening Primrose Oil, Vitex agnus-castus, flaxseed), and

lifestyle modifications (e.g., dietary changes, supportive bras).

- C (Comparisons): Placebos, standard care, other treatments, or varying dosages.
- O (Outcome): Reduction of cyclic mastalgia.

2-2. Inclusion and exclusion criteria

This review included randomized controlled trials (RCTs) and both randomized and non-randomized clinical studies (retrospective or prospective). Due to the limited number of RCTs published, other types of clinical studies were included. Pilot, preliminary, and case report studies were excluded due to their limited sample size and higher risk of bias. Only studies published in English up to August 2021 were considered.

2-3. Information sources

A systematic search of electronic databases (Scopus, Cochrane Central Register of Controlled Trials, EMBASE-Ovid, and Medline Complete) was conducted to identify randomized controlled trials and non-randomized prospective or retrospective clinical studies published up to August 2021.

2-4. Search

To investigate the effects of phytoestrogens on cyclic mastalgia, two reviewers independently searched electronic databases using the following keywords: (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).

2-5. Study selection

Potential studies were identified through a database search. Abstracts were screened for eligibility, and full-text articles were obtained and assessed. A final list of included studies was compiled. Two reviewers independently performed these steps in duplicate, with a third reviewer resolving any disagreements.

2-6. Data collection process

We developed a custom data extraction form and used it for each study. Two reviewers independently collected data, which was then combined and compared for accuracy. Any discrepancies were resolved by a third reviewer.

2-7. Data items

Two authors independently used a pre-designed checklist to extract relevant data, including authors, year of publication, patient age, study location (country), type of intervention, dropout rate, study instrument, number of subjects in case and control groups, and main results (**Table 1**).

2-8. Risk of bias in individual studies

The quality of articles was assessed using the Jadad scale (9). This scale evaluates three main domains: randomization (method and appropriateness), blinding (method and suitability), and dropouts/withdrawals. The Jadad scale assigns a score from 0 to 5 (not 0 to 1). Two researchers independently assessed each item, and disagreements were resolved by a third party (**Table 2**). Intention-to-treat analysis and baseline comparability were not part of the original Jadad scale assessment, but were included in the evaluation.

2-9. Data analysis

Data analysis was performed using Comprehensive Meta-Analysis Version 2.0 (CMA 2.0). Heterogeneity between studies was assessed using Cochran's Q test and the I^2 statistic, with a p-value less than 0.1 indicating significant heterogeneity. The I^2 statistic estimates the percentage of total variation across studies that is due to true heterogeneity rather than chance1.

Following the guidelines of Higgins et al. (7), I^2 values were interpreted as low (<25%), moderate (25-75%), or high (>75%) heterogeneity. Based on the heterogeneity assessment, a random-effects model was used if the I^2 statistic was 25% or higher; otherwise, a fixed-effect model was employed. Forest plots were used to graphically display the results of the meta-analysis, with the size of each square representing the study's weight and the horizontal lines indicating the 95% confidence interval (CI) for each study's effect size13. Publication bias was assessed using funnel plots in conjunction with Egger's and Begg's tests (10).

2-10. Ethical considerations

Ethical approval was not sought for this study because it involved secondary analysis of publicly available, anonymized data. We maintained ethical standards by acknowledging all sources appropriately, respecting copyright, and clearly outlining our methodology.

3- RESULTS

Characteristics of the eight included studies are presented in **Table 1**. The study selection process is illustrated in **Figure 1**. Quality assessment results for all included studies are summarized in **Table 2.**

Table-1: General characteristics of included studies (n=8).

Authors, Year, Country, (Reference)	Age (years)	Intervention/Control Group Size (n)	Type of intervention		Duration	Drop out (%)	Assessment tool	Results
			Case group	Control group				
Ingram et al., 2002, Australia (11)	40 ± 6	Isoflavones 40mg: 5 Isoflavones 80mg: 7 Placebo: 6	Red clover extract containing 40 mg isoflavones + antioxidants (1 tablet daily)	Placebo containing antioxidants and excipients	3 months	78.3	VAS	Pain reduction: Placebo (13%), Isoflavones 40mg (44%), Isoflavones 80mg (31%)
Mirghafourvand et al., 2016, Iran (12)	18–45	Flaxseed: 53 Vitex agnus: 53 Placebo: 53	Flaxseed powder 25g daily *Vitex agnus-castus* tablet (2-3 g) daily	Placebo	2 months	0	Cardiff Breast Pain Chart	Significant reduction in breast pain severity and duration in both intervention groups.
Mirmolaei et al., 2016, Iran (13)	15-49	*Vitex agnus* syrup: 36 Placebo syrup: 36	*Vitex agnus-castus* syrup (8 ml) mixed with water and honey, daily	Syrup (10 ml) containing oral paraffin, honey, and water, daily	3 months (5 month follow-up)	6.9	VAS & Short Form McGill Pain Questionnaire	*Vitex agnus* significantly relieves pain, especially in women with moderate to severe breast pain using supportive bras and good nutrition.
Mirmolaei et al., 2017, Iran (14)	15-49	*Nigella Sativa* syrup: 36 Placebo syrup: 36	*Nigella Sativa* syrup (10 ml) containing 5ml *Nigella Sativa*, honey, and water, daily	Syrup (10 ml) containing oral paraffin, honey, and water, daily	3 months (5 month follow-up)	9.7	VAS & Short Form McGill Pain Questionnaire	*Nigella Sativa* significantly reduces pain compared to placebo.

Rajaby Gharaiy, 2017, Iran (15)	Cinnamon: 26.2 ± 5.58 Control: 25.76 ± 4.65	Cinnamon: 37 Control: 37	Cinnamon capsules 400 mg (3 capsules daily)	Placebo capsules	2 months	0	Cardiff Breast Pain Chart	Cyclical breast pain severity significantly less in the cinnamon group than the control group.
Saghafi et al., 2018, Iran (16)	Chamomile: 26 ± 7.2 Placebo: 29 ± 6.8	Chamomile: 30 Placebo: 30	Chamomile drops (15 drops daily)	Placebo drops (distilled water)	2 months	0	VAS & Breast Pain Chart (BPC)	Chamomile was well-tolerated, safe, and effective for treating mild to moderate mastalgia.
Vaziri et al., 2014, Iran (4)	29.63 ± 7.05	Flaxseed bread: 61 Omega-3: 60 Wheat bread: 60	Flaxseed bread (containing 40 g wheat flour), daily	Omega-3 fatty acids pearl (180 mg eicosapentaenoic acid, 120 mg docosahexaenoic acid), daily Wheat bread (containing 40 g wheat flour), daily	2 months	9.04	VAS	Flaxseed bread diet was an effective approach in decreasing cyclical mastalgia.
Sekhavat et al., 2009, Iran (17)	*Vitex agnus*: 30.2 ± 12.1 Control: 29.9 ± 11.7	*Vitex agnus-castus*: 55 Control: 62	*Vitex agnus-castus* drops (60 drops containing 3.5 mg), daily	Placebo	3 months	2.5	VAS	Pain significantly decreased in *Vitex agnus-castus* group compared to placebo.

VAS: Visual analogue scale.

Table-2: Quality assessment of studies using the Jadad scale (9).

Author, Year, (Reference)	Randomization			Blinding			Patient Account
	Mention Randomization	Method: Appropriate	Method: Inappropriate	Concealment Mention blinding	Method: Appropriate	Method: Inappropriate	
Ingram et al. (2002)	Yes	Unclear	Yes	Yes	Yes	Unclear	Yes
Mirghafourvand et al. (2016)	Yes	Unclear	Yes	Yes	Yes	Unclear	Yes
Mirmolaei et al. (2016)	Yes	Unclear	Yes	Yes	Yes	Unclear	Yes
Mirmolaei et al. (2017)	Yes	Unclear	Yes	Yes	Yes	Unclear	Yes
Rajaby Gharaiy et al. (2017)	Yes	Unclear	Yes	Yes	Yes	Unclear	Yes
Saghafi et al. (2018)	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Vaziri et al. (2014)	Yes	Unclear	No	Yes	Yes	Unclear	No
Sekhavat et al. (2009)	Yes	Unclear	Yes	Yes	Yes	Unclear	Yes

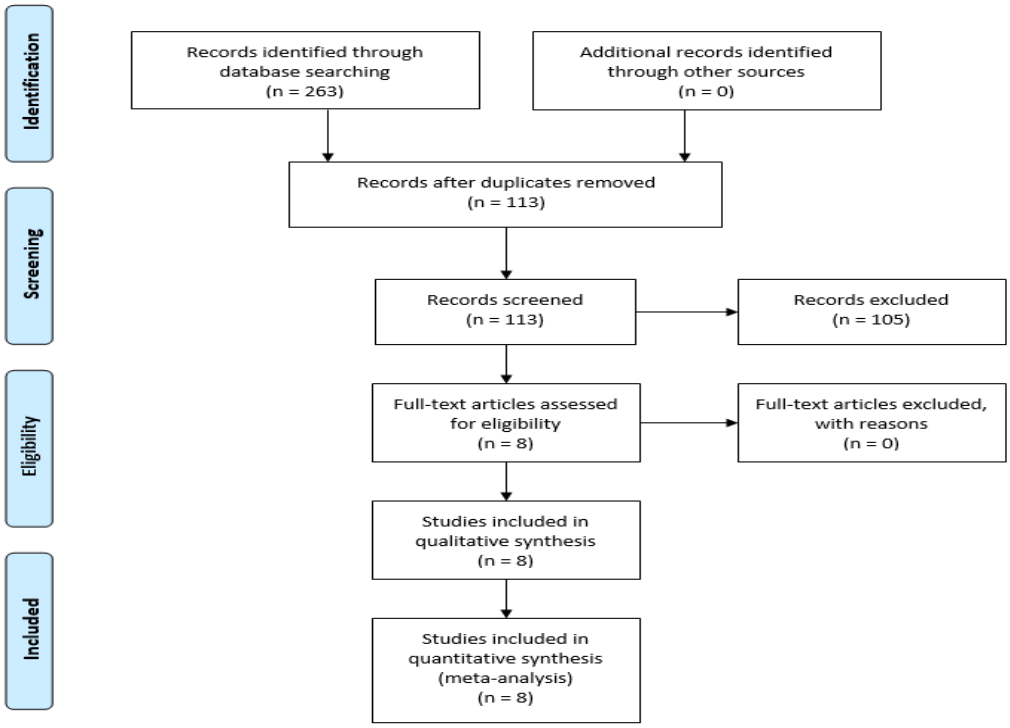

Fig.1: PRISMA flowchart.

This meta-analysis examined the effect of phytoestrogens, derived from ten different plants, on cyclic mastalgia, based on data from eight studies. Cochran's Q test indicated significant heterogeneity between the study results, justifying the use of a random-effects model rather than a fixed-effects model. The standardized mean difference (SMD) between the intervention and control groups was -1.40 (95% CI: -1.93 to -0.88), a statistically significant result ($p < 0.001$) that supports the effectiveness of phytoestrogens in treating cyclic mastalgia (**Figure 2**).

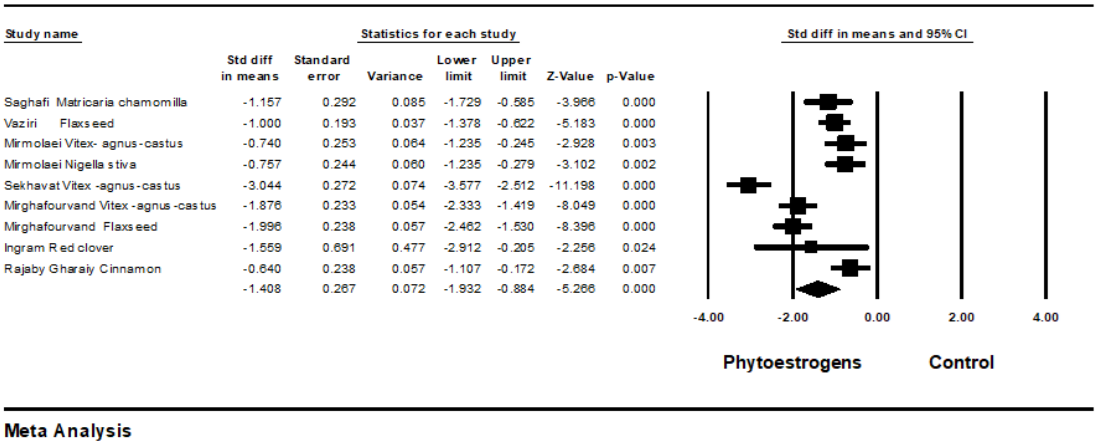

Fig. 2: Effects of phytoestrogens on cyclic mastalgia. Forest plot showing 95% confidence intervals (lines), point estimates (squares [■], size = study weight), and overall effect (diamond [♦]).

Due to significant heterogeneity between studies ($p < 0.001$; $I^2 = 89.3\%$), a sensitivity analysis was conducted to assess the influence of each individual study on the overall result. No single study significantly altered the final outcome or reduced the heterogeneity. Subgroup analysis was then performed based on the type of treatment (Flaxseed and Vitagnus). Analysis of the two studies using Flaxseed [Mirghafourvand et al. 2016 (12); Vaziri et al. 2014 (4)] revealed that women in the Flaxseed group reported significantly less pain than the control group (SMD: -1.48; 95% CI: -2.46 to -0.512) (**Figure 3**).

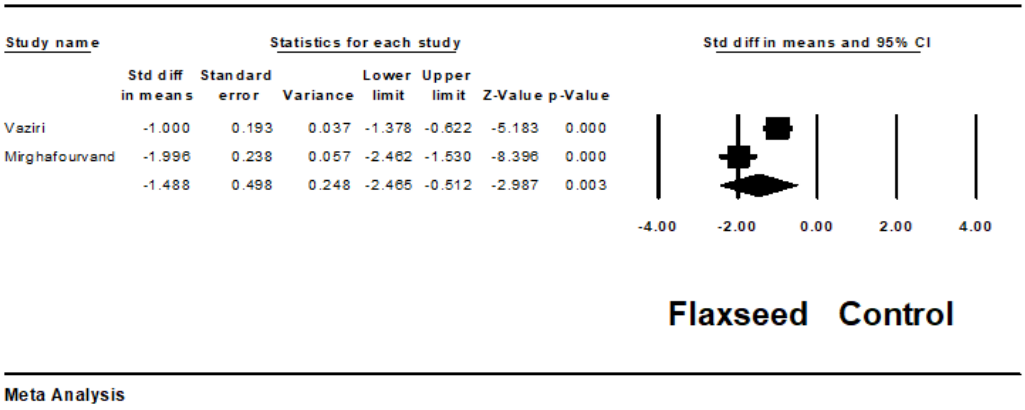

Fig. 3: Effects of Flaxseed on cyclic mastalgia. Forest plot showing 95% confidence intervals (horizontal lines), point estimates (squares [■] sized by study weight), and overall effect (diamond [♦]).

Given the high heterogeneity between studies ($p < 0.001$; $I^2 = 90.56\%$), sensitivity analysis was performed but did not identify a specific source of the heterogeneity. Subgroup analysis of Vitex agnus-castus, based on three studies [Mirghafourvand et al. 2016 (12); Mirmolaei et al. 2016 (13); Sekhavat and Zare Tarzejani 2009 (17)], showed a significant reduction in pain severity in the Vitagnus group compared to the control group (SMD: -1.78; 95% CI: -2.88 to -0.68; $p < 0.001$) (**Figure 4**).

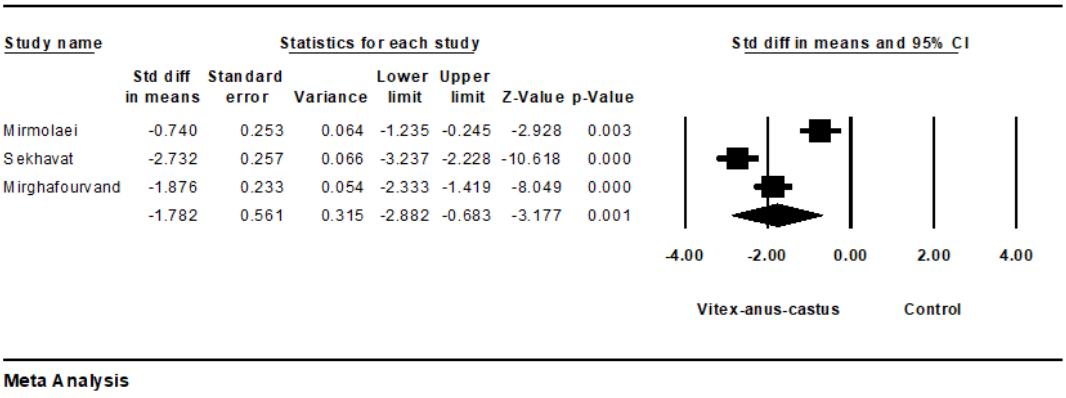

Fig. 4: Effects of Vitex agnus-castus on cyclic mastalgia. Forest plot showing SMD and 95% confidence intervals. Square size (■) reflects study weight; diamond (♦) represents the pooled effect estimate.

Given the high heterogeneity between studies ($p < 0.001$; $I^2 = 93.51\%$), sensitivity analysis was conducted to evaluate the influence of each study on the final result and the degree of heterogeneity, identifying potential sources of heterogeneity. However, no single study significantly affected the final result or the degree of heterogeneity. Publication bias was assessed using Egger's test (intercept: -1.92, $p = 0.89$) and Begg's test ($p = 0.630$), which were not statistically significant. The funnel plot is shown in **Figure 5**.

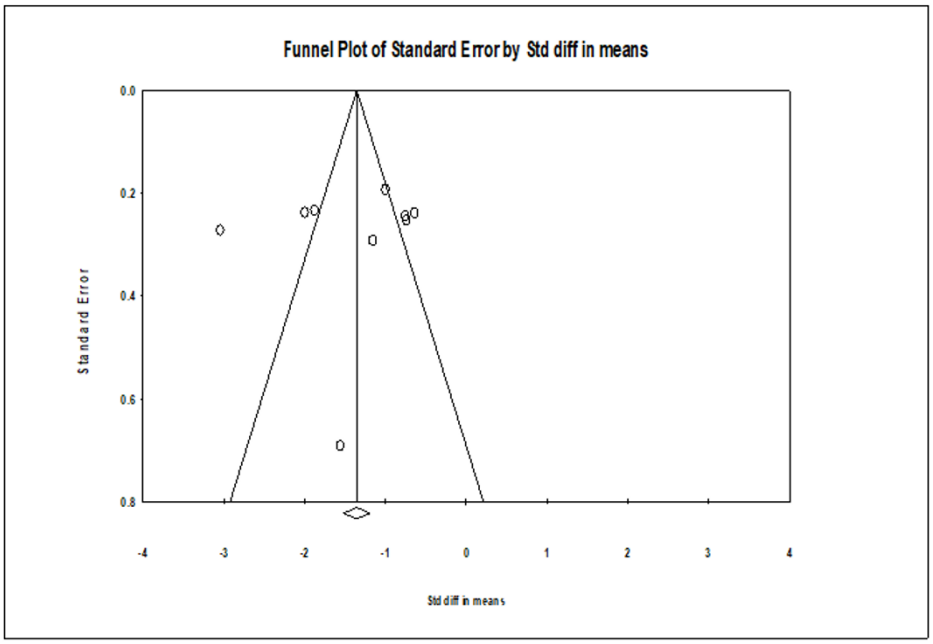

Fig. 5: Funnel plot assessing publication bias in the meta-analysis of phytoestrogens for mastalgia.

4- DISCUSSION

The results of the meta-analysis showed that phytoestrogens (SMD: -1.40; 95% CI: -1.93 to -0.89) and their subgroups, such as flaxseed (SMD: -1.48; 95% CI: -2.46 to -0.51), and Vitex agnus-castus (SMD: -1.78; 95% CI: -2.88 to -0.68; $p < 0.001$), were significantly effective in reducing the severity of cyclic mastalgia. However, the heterogeneity index across all studies was significantly high, falling within a moderate to high range. Additionally, Nigella sativa, chamomile, red clover, and cinnamon also significantly reduced the severity of cyclic breast mastalgia. Phytoestrogens may have beneficial effects on improving cyclic breast mastalgia; however findings from this study should be interpreted cautiously due to high heterogeneity between studies and limitations such as few studies with small sample sizes.

Linum usitatissimum (Linn.), commonly known as flaxseed or linseed, contains large amounts of plant lignans belonging to the phytoestrogen family and possesses antioxidant properties (references 1, 2, 4, 17). Flaxseed also contains polyunsaturated fatty acids, which can aid in synthesizing omega-3 fatty acids (1, 17). It inhibits aromatase activity, thereby reducing estrogen production. The basic structure of phytoestrogens is similar to that of estradiol and selective estrogen receptor modulators (SERMs), including tamoxifen, which is used to treat mastalgia (4, 18). One of the most notable studies on the effect of flaxseed on cyclical mastalgia was conducted by Goss et al., whose findings align well with those of this study.

According to their results, flaxseed has been proposed as a first-line treatment for mastalgia (19). Given that flaxseed is affordable, tolerable, and widely available (4), it can be prescribed to various target groups across different physical and economic conditions. Due to its fewer side effects compared to chemical drugs, women can safely use flaxseed to treat mastalgia during premenstrual syndrome (3). Additionally, flaxseed may act as a protective factor against breast cancer in women (20). Consequently, studies recommend consuming 25 grams of flaxseed daily for premenopausal women (21).

In a randomized controlled trial involving 159 women with cyclical mastalgia, the results showed significant improvements in breast pain in both intervention groups during the first and second months following intervention. The mean score of patients who received 25g daily flaxseed powder was significantly lower in the first month after intervention compared to those who received 3.2–4.8 mg daily Vitex agnus-castus tablets (21). However, a study by Jaafarnejad et al. found that flaxseed, vitamin E, and evening primrose oil did not differ significantly in terms of mastalgia treatment efficacy (22). In contrast, Vaziri et al. (2014) reported that flaxseed was more effective than omega-3 fatty acids for controlling mastalgia (4).

Vitex agnus-castus is an herbal medicine native to the Mediterranean region (23), known for its anti-prolactin activity and effectiveness in treating premenstrual syndrome and hypermenorrhea; it can serve as an alternative to complex treatments like danazol (24). In a randomized, placebo-controlled double-blind trial examining a solution containing Vitex agnus-castus extract on patients with cyclical mastalgia, significant pain relief differences were observed between Vitex agnus-castus and placebo after one or two courses of treatment (25). Another clinical trial administered 60 drops of Vitex agnus-castus over three months to menstruating women experiencing breast pain; at treatment's end, approximately 88.4% responded positively without adverse effects or drug side effects being reported (24). A review study on herbal medicines' impact on mastalgia found stronger evidence supporting use of Vitex agnus-castus and Vitamin E for treating this condition (18). Herbal remedies have become common methods for both treating and preventing mastalgia as well (6).

Chamomile, cinnamon, and red clover are recognized globally for their phytoestrogenic properties. These plants may also effectively reduce mastalgia (1). A study evaluating the effectiveness of chamomile in managing cyclical mastalgia found that administering chamomile three times daily for two months, at a dose of five drops each time, was a tolerable, safe, and effective treatment for women with mild to moderate mastalgia (16). Other studies have indicated that cinnamon may also reduce mastalgia (15). In a study by Mirmolaei et al., 72 women with cyclical mastalgia, referred to the Center for Breast Cancer at Jihad of Tehran University in 2014-2015, were randomly assigned to either an intervention group (fennel flower syrup, n=36) or a placebo group (paraffin oil syrup, n=36). Pain intensity was measured using a visual analog scale (VAS) and the short-form McGill Pain Questionnaire (SF-MPQ) two months before and three months after the intervention. While the SF-MPQ showed no significant difference between the fennel flower and placebo groups, the VAS scores indicated a significant difference ($p=0.002$). The results suggest that fennel flower was more effective than the placebo in alleviating pain intensity; therefore, it may be prescribed as an adjunct therapy for cyclical mastalgia (26).

Thymoquinone is a key constituent of fennel flower, potentially contributing to

its anti-inflammatory, antioxidant, anti-oxidative stress, and anti-cancer properties. The chemical composition of fennel flower essential oil consists of 17% saturated fatty acids and 82.5% unsaturated fatty acids, with linoleic acid (55.6%), oleic acid (23.4%), and palmitic acid (12.5%) as its primary components. Scientific literature has reported that various compounds in fennel flower oil and hydroalcoholic extract possess immune-boosting, antioxidant, anti-inflammatory, and antihistamine properties. Additional studies suggest that this plant may also exhibit antimicrobial, gastrointestinal disorder-healing, blood pressure-lowering, blood glucose-lowering, blood lipid-lowering, and anti-cancer effects, as well as protective properties for the liver, kidneys, nervous system, and cardiovascular system. Furthermore, traditional medicinal use of this plant at appropriate dosages has not been associated with significant side effects (26). Ghamdi-Al's study in rats has demonstrated the analgesic properties of fennel flower (27), supporting the confirmed effectiveness of fennel flower in improving mastalgia, aligning with findings from animal studies.

4-1. Study limitations

A primary limitation of this study was the poor methodological quality of some included articles. Deficiencies included the lack of, or inadequate reporting of, random allocation sequences and blinding. Future studies should be designed and reported according to CONSORT guidelines to address these issues. Additional limitations were the small number of studies and their small sample sizes, highlighting the need for further research with larger sample sizes in this area.

5- CONCLUSION

The current evidence indicates that phytoestrogens—such as isoflavones, *Nigella sativa*, cinnamon, chamomile tea, *Vitex agnus-castus*, and flaxseed—may provide significant relief from cyclic mastalgia. Although the overall trend across studies supports their beneficial effects, heterogeneity in study design and outcomes warrants cautious interpretation. Subgroup analyses particularly highlight flaxseed and *Vitex agnus-castus* as potentially more effective in reducing cyclical breast pain. Given their favorable safety profile compared to conventional pharmacological treatments, phytoestrogens may serve as a promising adjunct or alternative therapeutic option for affected women.

Nevertheless, limitations such as small sample sizes, inconsistent methodologies, and variable formulations constrain the strength of these conclusions. Future research should prioritize well-designed, large-scale, randomized controlled trials to confirm efficacy, clarify optimal dosages and preparations, and elucidate underlying mechanisms. In summary, phytoestrogens demonstrate potential as a complementary approach in managing cyclic mastalgia, pending stronger and more consistent clinical evidence.

6- CONFLICT OF INTEREST: None.

7- REFERENCES

1. Aydin İ, Baltaci D, Trkyilmaz S, NC M. Comparison of Vitex Agnus Castus with Meloxicam and Placebo in Treatment of Patients with Cyclical Mastalgia. Duzce Medical Journal. 2012;14:29.

2. Godazandeh G, Ala S, Motlaq TM, Sahebnasagh A, Bazi A. The comparison of the effect of flaxseed oil and vitamin E on mastalgia and nodularity of breast fibrocystic: a randomized double-blind clinical trial. Journal of Pharmaceutical Health Care and Sciences. 2021;7(1):1-8.

3. Sourinejad, H., Raisi Dehkordi, Z., Beigi, M., Adibmoghaddam, E., Hadian, M. The Use of Flaxseed in Gynecology: A

Review Article. Journal of Midwifery and Reproductive Health, 2019; 7(2): 1594-1614.

4. Vaziri F, Zamani Lari M, Samsami Dehaghani A, Salehi M, Sadeghpour H, Akbarzadeh M, Zare N. Comparing the effects of dietary flaxseed and omega-3 Fatty acids supplement on cyclical mastalgia in Iranian women: a randomized clinical trial. Int J Family Med. 2014;2014:174532.

5. Parveen S, Sarwar G, Ali M, Channa GA. Danazol versus oil of evening primrose in the treatment of mastalgia. Pak J Surg. 2007;23(1):10-13.

6. Singh D, Gupta R, Saraf SA. Herbs–are they safe enough? An overview. Critical reviews in food science and nutrition. 2012;52(10):876-98.

7. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. Statistics in medicine. 2002 Jun 15;21(11):1539-58.

8. Kurzer MS, Xu X. Dietary phytoestrogens. Annu Rev Nutr. 1997;17:353-81. doi: 10.1146/annurev.nutr.17.1.353.

9. Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ, McQuay HJ. Assessing the quality of reports of randomized clinical trials: is blinding necessary? Control Clin Trials. 1996 Feb;17(1):1-12.

10. Egger M, Smith GD, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ. 1997;315(7109):629-34.

11. Ingram D, Hickling C, West L, Mahe L, Dunbar PJTB. A double-blind randomized controlled trial of isoflavones in the treatment of cyclical mastalgia. 2002;11(2):170-4.

12. Mirghafourvand M, Mohammad-Alizadeh-Charandabi S, Ahmadpour P, Javadzadeh Y. Effects of Vitex agnus and Flaxseed on cyclic mastalgia: A randomized controlled trial. Complementary therapies in medicine. 2016; 24: 90-5.

13. Mirmolaei S, Olfatbakhsh A, Fallahhosseini H, Kazemnejad E, Sotodeh A. The Effect of Vitagnus on Cyclic Breast Pain in Women of Reproductive Age. Journal of Babol University of Medical Sciences. 2016;18(9):7-13.

14. Mirmolaei ST, Olfatbakhsh A, Falah Huseini H, Kazemnezhad Leyli E, Sotoodeh Moridiani AJHJ. The effect of Nigella Sativa syrup on the relief of cyclic mastalgia: A triple-blind randomized clinical trial. 2017;23(1):33-43.

15. Rajaby Gharaiy N, Shahnazi M, Yavari Kia P, Javadzadeh Y. The Effect of Cinnamon on Cyclical Breast Pain. Iran Red Crescent Med J. 2017 June; 19(6):e26442.

16. Saghafi N, Rhkhshandeh H, Pourmoghadam N, Pourali L, Ghazanfarpour M, Behrooznia A, et al. Effectiveness of Matricaria chamomilla (chamomile) extract on pain control of cyclic mastalgia: a double-blind randomised controlled trial. Journal of Obstetrics and Gynaecology. 2018;38(1):81-4.

17. Sekhavat L, Zare Tarzejani T. The effect of vitex agnus-castus on mastalgia in women. ISMJ. 2009;11(2):147-52.

18. Sheidaei S, Irani M, Ghazanfarpour M. The effect of Herbal Medicines and Supplements on Mastalgia: A systematic review and meta-analysis of clinical trials in Iran. The Iranian Journal of Obstetrics, Gynecology and Infertility. 2019;22(3):87-98.

19. Goss P, Li T, Theriault M, Pinto S, Thompson L. Effects of Dietary Flaxseed in Women with Cyclical Mastalgia. Breast Cancer Research and Treatment. 2000;64(1):49.

20. Flower G, Fritz H, Balneaves LG, Verma S, Skidmore B, Fernandes R, Kennedy D, Cooley K, Wong R, Sagar S, Fergusson D, Seely D. Flax and Breast Cancer: A Systematic Review. Integr Cancer Ther. 2014 May;13(3):181-92.

21. Babushkina EA, Belokopytova LV, Grachev AM, Meko DM, Vaganov EA. Variation of the hydrological regime of Bele-Shira closed basin in Southern Siberia and its reflection in the radial growth of Larix sibirica. Regional Environmental Change. 2017;17(6):1725-37.

22. Jaafarnejad F, Hosseini SF ,Mazlom SR, Hami M. Comparison of the effect of fish oil and vitamin E on the duration of Cyclic mastalgia. Evidence Based Care. 2013;3(1):69-76.

23. Salati SA, Alhumaid AA. Mastalgia: A narrative literature review of current understanding and management .East and Central African Journal of Surgery. 2018;23(1):42-51.

24. Cerqueira RO, Frey BN, Leclerc E, Brietzke E. Vitex agnus castus for premenstrual syndrome and premenstrual dysphoric disorder: a systematic review. Arch Womens Ment Health. 2017 Dec;20(6):713-719. doi: 10.1007/s00737-017-0791-0. Epub 2017 Oct 23. PMID: 29063202.

25. Zafar A, Rehman A. Topical diclofenac versus oral diclofenac in the treatment of mastalgia ñ a randomized clinical trial. Rawal Medical Journal. 2013;38(4):371-7.

26. Mirmolaei ST, Olfatbakhsh A, Falah Huseini H, Kazemnezhad Leyli E, Sotoodeh Moridiani A. The effect of Nigella Sativa syrup on the relief of cyclic mastalgia: A triple-blind randomized clinical trial .Hayat Journal. 2017;23(1):33-43.

27. Al-Ghamdi M. The anti-inflammatory, analgesic and antipyretic activity of Nigella sativa. Journal of ethnopharmacology. 2001;76(1):45-8.