Review Article



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PHYTOTHERAPEUTIC MANAGEMENT OF CYCLIC MASTALGIA – A REVIEW

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ABSTRACT

Background: Mastalgia is one of the most prevalent breast disorders in females. It has been treated using a variety of natural plant medications. The purpose of this article is to provide a quick overview on plant-based treatments for cyclic-mastalgia based on peer-reviewed literature and to summarize the clinical trials that have been conducted. **Materials and Methods:** The data used in the compilation of this review article were gathered from peer-reviewed literature derived from various websites, including PubMed, PubMed Central, Scopus, ScienceDirect, Google Scholar, and Medline. Articles available in English, including randomized controlled trials, observational studies, and review articles, were included. The terms used for the search included "mastalgia", "mastodynia", "breast pain", "herbal", "cyclic mastalgia", "herbal," and "medicinal plants." **Results:** A wide range of medicinal herbs has been reported in the literature to be effective in the treatment of cyclic mastalgia. **Conclusion:** Mastalgia can be treated using plant-based products, but more research is needed to understand their potential side effects and drug interactions. Plant products shouldn't be rejected as useless nor assumed to be absolutely safe merely because they are natural.

Keywords: Cyclic Mastalgia, Mastodynia, Breast Pain, Plant Products, Phytotherapeutics

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INTRODUCTION

Mastalgia (also known as breast pain or mastodynia) is one of the most prevalent breast symptoms among women of reproductive age, with prevalence estimates ranging from 41% to 79 percent in the literature [1-2]. Mastalgia can be classified into three types: cyclic, noncyclical, and

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extra-mammary. Cyclic mastalgia is the most common, accounting for almost two-thirds of all mastalgia occurrences. Cyclic mastalgia appears one to two weeks before menstruation and corresponds to the luteal phase of the menstrual cycle. It is most common in women in their third and fourth decades of life. Sharp, stabbing, heavy, agonizing, profound soreness, or throbbing pain is common. It's usually bilateral, though one side may be more severe than the other, and it radiates to the upper arm and axilla. The pain is relieved when menstruation begins [2].

In up to 22% of patients, cyclic mastalgia may resolve spontaneously, or it may cease during pregnancy. However, in the majority of instances (up to 65 %), the illness lasts until menopause [1-2]. Mastalgia can be severe enough to negatively influence one's quality of life by interfering with everyday routines such as sexual activity (41%), physical activity (35%), and socializing (10%).

Despite the apparent link to the menstrual cycle, the etiology of cyclic mastalgia is uncertain. Hormonal assays of estrogen, progesterone, and prolactin have also revealed inconsistencies The following are some of the primary etiological agents mentioned in the literature as depicted in Figure 1.

Endocrine abnormalities

i. Hormonal imbalance is caused by increased estrogen release and low progesterone production during the luteal phase of the menstrual cycle [3]. ii. Hyperprolactinemia: Mastalgia patients have significantly higher levels of prolactin than the healthy controls [4-5].

Miscellaneous factors

Psychoneurosis: Treatment-resistant cyclic mastalgia has been associated to depression, anxiety, a history of emotional abuse, and somatization, and may cluster with unexplained pain syndromes [6-7].

Aberration in lipid metabolism

According to certain studies, patients with cyclic mastalgia have greater amounts of saturated fatty acids and a deficiency in gamma-linolenic acid (GLA), which makes their breast tissue excessively sensitive to normal hormone levels and causes pain [8].

Smoking

Cigarette smoking has been shown in certain studies to exacerbate breast pain by raising adrenaline levels in the breast [3].

Caffeine and methylxanthines

Caffeine and methylxanthines found in tea, coffee, cola, and chocolate may interfere with adenosine triphosphate breakdown, causing breast cell overstimulation and discomfort, according to several clinical and laboratory studies [9].

Mastalgia treatment options range from nonpharmacologic measures such as explanation/reassurance, sports bras, dietary changes, and exercise to a multitude of pharmacological remedies. A concept of safe integration of effective herbal therapy into conventional medical practices has emerged in recent years. There has been a lot of

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Figure 1: Etiological factors of cyclic mastalgia

interest in developing medicinal plant-based remedies for mastalgia management [10].

The purpose of this study is to provide an overview of recent peer-reviewed literature on this aspect of mastalgia therapy.

MATERIAL AND METHODS

Through PubMed, PubMed Central, Scopus, ScienceDirect, Google Scholar, and Medline Internet searches, data for this study was gathered from randomized controlled trials, observational studies, and review articles, with a focus on studies published in the English language over the last two decades. The terms "mastalgia," "mastodynia," "breast pain," "cyclic mastalgia," "herbal," and "Medicinal Plants" were used in the search. Articles published after 2000 were preferred, however, if no recent reference was available on a topic of interest, older articles were chosen. Articles written in languages other than English were excluded.

REVIEW OF LITERATURE

Phytotherapeutic Agents for Cyclic Mastalgia

According to the literature review, the following plant products have been documented for the treatment of cyclic mastalgia:

I. Phytoestrogens

Phytoestrogens (dietary estrogens) are a broad category of naturally occurring nonsteroidal plant chemicals that generate mildly estrogenic biological responses by mimicking or altering the activities of endogenous estrogens, mainly through binding to estrogen receptors [1]. Phytoestrogens can be generally classified

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into the following groups: isoflavones, coumestans, and lignans [2] . Isoflavones, which have been the most extensively studied phytoestrogens for mastalgia, are found predominately in Glycine max (Soybeans) and Trifolium pratense (Red Clover).

Genistein, daidzein and glycitein are the most active isoflavones found in soy beans. Red clover contains isoflavonoid glucoside, including ononin and sissotrin, and isoflavone aglycones, including Biochanin A and formononetin [11].

Ingram et al. [12] in a small, double-blind, randomized, controlled trial demonstrated that isoflavones led to a significant improvement in cyclic mastalgia (13% for placebo, 44% for 40 mg of isoflavones per day, and 31% for 80 mg per day). McFadyen et al. [13], however did not get unequivocal results that could support the use of soya isoflavones.

II. Linum usitatissimum

Flaxseed (Linum usitatissimum) is rich in unsaturated essential fatty acids (mostly omega-3) and lignans. In a double-blind, placebo-controlled trial, Goss et al. [14] investigated the effect of dietary flaxseed in 116 patients with severe cyclic mastalgia. The treatment group was given 25 grams of flaxseed per day and was tracked for up to four menstrual cycles. The flaxseed group experienced a significant reduction in breast pain.

In their respective trials, Vaziri et al. [15] and Godazandeh G et al. [16] found that a flaxseed bread diet is an effective technique for reducing cyclical mastalgia and could be administered to women as a simplistic treatment with few problems.

III. Nigella sativa

Nigella sativa (also known as fennel flower seeds, black cumin, or black seeds) is a widely utilized medicinal plant in several traditional medical systems. Thymol, dithymoquinone, thymoquinone, thymohydroquinone, and several alkaloids, Nigellamine notably are the active components in Nigella sativa aqueous extract [17-18]. Nigella sativa seeds are a rich source of essential and unsaturated fatty acids, including linoleic acid and oleic acid. In addition, Nigella sativa oils exert analgesic effects through kappa (k) and mu (μ)1 supraspinal cord receptors [19]. Huseini et al. [20], in a randomized, triple-blind, active, and placebo-controlled clinical trial, applied 600 mg of Nigella sativa seed oil twice a day for two months in 52 enrolled cases of cyclic mastalgia and compared it with topical diclofenac (20 mg twice a day) (n = 51) and placebo (n = 53). They concluded that topical Nigella sativa seed oil is safe, more effective than placebo, and has clinical effectiveness comparable to topical diclofenac in treating cyclic mastalgia.

Mirmolaei et al. [21] in a similar triple-blind randomized clinical trial, 65 women with cyclic mastalgia enrolled randomly into two groups: the intervention group (Nigella sativa=36) and placebo group (oral paraffin=36). The intervention group was administered 10 ml of Nigella Sativa syrup, whereas the placebo was administered 10 ml of liquid paraffin. N Sativa group felt

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significant relief in pain (P=0.002) as assessed by the Visual Analogue Scale (VAS). However, when a McGillsummarized questionnaire with fifteen items addressing emotional and spiritual components of pain was used, the results were statistically insignificant.

IV. Vitex agnus-castus

Vitex agnus-castus (also known as vitex, chaste-tree, chaste berry, Abraham's balm, lilac chaste tree, or monk's pepper) is a deciduous shrub native to Mediterranean Europe and Central Asia that has recently been suggested as an effective alternative phytotherapeutic agent in the treatment of mastalgia in recent studies.

V. Agnus-castus fruit extract is thought to include a group of structurally related diterpenoids that block the pituitary gland's dopamine-2 receptors, suppressing latent hyperprolactinemia. Normally, patients release more than physiologic amounts of prolactin in response to stressful situations and during deep sleep phases due to the insufficient inhibitory effect of dopamine on the pituitary gland, which appears to stimulate the mammary gland. The cyclic mastalgia is relieved as a result of the induced hormonal shift [22].

The adverse events with V. agnus-castus treatment have been found to be mild and reversible. Webster et al. [23] suggested on the basis of their experiments that the therapeutic effects of V. agnus-castus are due to opioidergic mechanisms through the activation of μ - and δ -, but not κ -opioid

(MOR, DOR, but not KOR) receptor subtypes.

Carmichael [24] conducted a systematic review of the data from randomized and nonrandomized trials on the efficacy and safety of V. agnus-castus in the treatment of mastalgia and came to the conclusion that V. agnus-castus can be considered an effective alternative phytotherapeutic agent. Dinc and Coskun [25] enrolled 114 premenopausal cyclic mastalgia patients under the age of 40 and studied them prospectively after separating them into two treatment groups: V. agnus-castus extract (Group 1) and flurbiprofen (Group 2). Both of these drugs were shown to greatly reduce complaints and have manageable side effects.

Mirmolaei et al. [26] studied 67 women with cyclic mastalgia in a triple-blind controlled clinical trial. Women were randomly assigned to one of two groups: intervention (34 patients received 8 ml of V. agnus-castus extract) or placebo (33 patients received 1 ml of edible paraffin), and they were provided with training and suitable nourishment. The pain was measured with Visual Analogue Scale (VAS) and McGill measuring devices two months before and three months after treatment. The findings indicated that V. agnus-castus could be employed as a lowcost, effective treatment for cyclic mastalgia In a recent systematic review and metaanalysis by Ooi et al. [27], including 25 studies (17 randomized control trials plus 8 nonrandomized trials), V. agnus-castus was found to be effective in relieving breast pain intensity and lowering the serum prolactin level in cyclic mastalgia patients (18-45

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years) with or without premenstrual syndromes. The typical dosage was 20-40 mg/day with a treatment duration of 3 months. V. agnus-castus is a safe and effective therapeutic option for cyclic mastalgia, according to the study, albeit more high-quality clinical trials are needed to increase the evidence basis.

V. Oenothera biennis

Oenothera biennis is commonly known as evening primrose (EPO), and its seeds are rich in essential fatty acids (70% linoleic acid and 8–14% gamma-linoleic acid).

Mastalgia can be caused by saturated fatty acid esters, which cause the breast epithelium to become hypersensitive to hormones in the bloodstream. EPO, on the other hand, may help to restore the saturated/unsaturated fatty acid balance and reduce steroid hormone sensitivity. Furthermore, gamma-linoleic acid is converted into homo gamma-linoleic acid, which is thought to block arachidonic acid metabolite synthesis, resulting in antiinflammatory actions. The use of EPO to treat mastalgia has been frequently described in the literature. However, the results are mixed.

Mahboubi, in 2019 [28], analyzed the literature to study the efficacy of O biennis in cyclic mastalgia. The results of his analysis confirmed the effectiveness of mastalgia. But it was stressed that immediate response should not be expected from it and that relief may be attained after regular use for up to 4 or 6 months.

Srivastava et al. [29], in their meta-analysis of randomized trials, found that EPO did not offer any advantage over a placebo in pain relief. Ahmad Adni et al. [30] on the other hand, in a recently published systematic review and meta-analysis of the efficacy of EPO for mastalgia treatment, concluded that EPO is a safe medication with similar efficacy for pain control compared to a placebo, topical NSAIDs, danazol, or vitamin E. Furthermore, as compared to a placebo or other therapies, EPO does not have any increased side effects such as nausea, abdominal bloating, headache or giddiness, increased weight gain, or altered taste.

Balci et al. [31] 2020 published the results of a study involving 1015 patients with mastalgia. They found that the therapeutic efficacy of EPO on mastalgia was significantly higher than that of paracetamol (p < 0.001). They also found hormone replacement therapy (HRT), IUD-withlevonorgestrel, iron deficiency, overt hypothyroidism, and Hashimoto thyroiditis (p < 0.01) were the factors that significantly decreased the efficacy of EPO. In the patients who did not respond to EPO treatment, iron or thyroid hormone replacement efficiently relieved mastalgia. Side effects (allergy, anxiety, blurred vision, constipation, and nausea) were rare and not statistically significant (p = 0.88). The study concluded that EPO could be used to treat mastalgia without significant side effects and that if treatment fails, the patient should be evaluated for potentially reversible factors that could be impeding EPO's efficacy.

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VI. Hypericum perforatum

Hypericum perforatum (known commonly as perforate St John's-wort) contains various chemicals, such as anthraquinone derivatives (Naphthodianthrones), flavonoids, fluoroglosinols, tannins, hyperforin, and hypericin.

In 2006, Pakgohar et al. [32] published the findings of a study in which 70 patients were randomly divided into two groups, each with 35 patients, and given thirty drops of Hypericum perforatum extract or placebo twice a day for at least a week before menstruation for two consecutive cycles. The Hypericum perforatum group showed a 75.6 % reduction in the intensity of mastalgia.

VII. Matricaria chamomilla (chamomile)

Matricaria chamomilla (commonly known as Chamomile) is a member of the Asteraceae/Compositae family and is represented by two common varieties, viz. German Chamomile (Chamomilla recutita) and Roman Chamomile (Chamaemelum nobile). The dried flowers of Chamomile approximately contain 120 secondary metabolites with medicinal properties, including 28 terpenoids and 36 flavonoids [33].

Saghafi et al. [34] evaluated 60 patients with cyclic mastalgia in a double-blind, randomized controlled clinical trial. The patients were randomly assigned to one of two groups: chamomile intervention (n = 30) or placebo (n = 30) and instructed to take five drops three times a day for two months. After two months, both groups (Chamomile and placebo) experienced considerable pain relief

(p.0001 and p =.048, respectively) as judged by the visual analog scale (VAS) and the breast pain chart (BPC), but the relief was statistically more significant with Chamomile (p =.007). Chamomile is a safe, efficient, and well-tolerated medication for women with mild to moderate mastalgia, according to the study.

Tester [35], on the other hand, criticized the study by Saghafi et al. [34], pointing out that the study did not specifically specify the dosing technique or make any mention of the extract's contents. In addition, Tester thought the method for calculating the pain scores was ambiguous. She believes that further research is needed, with better study design, methodology, and reporting, before any possible benefits of Chamomile in cyclic mastalgia can be recognized. Other plant products

There are certain additional plant preparations that have been reported to be effective in the treatment of Premenstrual Syndrome and accompanying mastalgia, though the evidence is sparse. Among these plants are Zingiber officinale, Curcuma longa, Citrus sinensis, Ginkgo biloba, Wheat germ, Echinosophora Platyloba, and Rosa damascene [2, 36].

Adverse Effects and Precautions

Plant products contain organic chemicals that, like conventional pharmaceuticals, can have side effects and interact with other treatments. It would be inappropriate if a physician prescribed a plant product without first thoroughly comprehending the pharmacology of the ingredients in that

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Herbs	Adverse effects
Linum usitatissimum	Nausea, bloating, gas, heartburn, or diarrhea; alteration of coagulation
	profile, allergic reactions
Nigella sativa	Allergic reaction, alteration of coagulation profile, sleepiness, nausea,
	heartburn, constipation; interactions with a wide range of drugs like
	antihypertensives, oral hypoglycaemics, antipsychotics, etc
Vitex agnus-castus	Nausea, headache, gastrointestinal disturbances, menstrual disorders,
	acne, pruritus, and erythematous rash.
Oenothera biennis	Nausea, heartburn, or diarrheaa; headache; deranged serum lipid profile
	and increased levels of transaminases
Hypericum perforatum	Photosensitivity, gastrointestinal symptoms, allergies, fatigue, and
	anxiety; interactions with a wide range of drugs including oral
	contraceptives
Matricaria chamomilla	Nausea, dizziness, and allergic reactions

Table 1: Adverse effects of common herbal medicine prescribed for Cyclic Mastalgia

product or if a physician recommended a plant product for which it is limited in vitro or in vivo data [37]. As a result, using plant products and conventional medications at the same time should be avoided until additional information is available.

To cite an example, Hypericum perforatum (St. John's wort) is associated with adverse effects like gastrointestinal symptoms, allergies, fatigue, and anxiety. It interacts with and changes the plasma levels of selective serotonin reuptake inhibitors (Sertraline, nefazodone) and hepatic enzyme inducers. It also enhances plasma clearance of micronutrients, including Vitamin D, and decreases the bioavailability of drugs like benzodiazepines (alprazolam, midazolam, triazolam, and quazepam) through induction of Cytochrome P450 3A4 (CYP3A4) metabolism [38]. It is also associated with increased metabolism of ethinyloestradiol, norethindrone, and keto desogestrel and may uterine bleeding and cause unwanted pregnancy due to the failure of oral contraceptives [39-42].

Similarly, while prescribing the plant products, due care should be exercised about the quality, just as is done in the case of conventional medications, as there is a possibility of irregularities like contamination with other plant species or even heavy metals and adulteration with synthetic drugs [43]. The adverse effects of commonly prescribed herbal medicine are summarized in Table 1.

FUTURE PERSPECTIVES

More research is needed to understand the mechanisms by which plant products and their constituents exert their therapeutic effects so that they can be safely and costeffectively integrated into modern medical practices for the treatment of cyclic mastalgia. Because of the large number of patients, there is a lot of room for research in this sector. Product quality can be improved

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by using good agricultural practices (GAPs), manufacturing final products according to good manufacturing procedures (GMPs), and conducting post-marketing quality assurance surveillance.

Proper integration of effective plant medicines into standard medical procedures will become feasible when more accurate pharmacological and clinical data, as well as information on the adverse effects of employing plant medicinal products, becomes available.

CONCLUSION

Various plant-based options have been mentioned in the literature for the treatment of cyclic mastalgia with variable efficacy. Adverse effects and drug interactions have also been reported, which include gastrointestinal upsets, allergic reactions, derangement of coagulation profile, and alteration of the effects of a wide variety of medications, including antihypertensives, hypoglycemics, diuretics. oral and antipsychotics. Plant products should not be rejected/condemned as useless simply because they are natural, nor should they be blindly presumed to be harmless. Larger scale prospective studies are needed to evaluate the efficacy and safety of plant products and the results of such studies would finally determine the place of the plant products in the treatment of mastalgia. Finally, herbal drugs need to be monitored for quality, purity, dosage, or packaging by agencies like U.S Food and Drug Administration.

SIGNIFICANCE STATEMENTS

This article is intended to arouse readers' curiosity in researching the literature on using plant products to treat mastalgia. Furthermore, the paper emphasizes the potential for plant-based products to have harmful effects and drug interactions.

CONFLICT OF INTEREST

No known competing financial interests or personal relationships could have appeared to influence the work reported in this review article.

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