

Cytoplasmic pollen extract for treatment of menopausal symptoms in breast cancer patients: a case series report

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Objective: Menopausal symptoms, such as hot flushes (HFs), night sweats, vaginal dryness, psychological symptoms, and sexual dysfunction are a significant issue in breast cancer (BC) survivors, especially in those with hormone receptor-positive (HR+) subtype. Since hormone replacement therapy (HRT) is not indicated in these patients due to its estrogenic activity, we sought to investigate the role of cytoplasmic pollen extract (Femal[®]) with non-estrogenic effects as an adjuvant treatment in BC women. **Methods:** This case series study included 12 women with HR+, eight with Luminal A and four with Luminal B cancers, with a median age of 47 years (range 37–53) who received cytoplasmic pollen extract for 3 months. Menopause symptomatology was monitored through the Menopause Rating Scale (MRS) at the beginning of the treatment (T₀) and at 90 days (T₃). Tolerance was evaluated by the European Organization for Research and Treatment of Cancer (EORTC) score. **Results:** After 3 months of treatment, all cases had an improvement in HFs, cardiac symptoms, irritability and anxiety symptoms. No side effects were found. Tolerance and compliance were excellent during the study. **Conclusions:** This observational study suggests that cytoplasmic pollen extract is well tolerated when administered to BC (HR+) women with contraindications to HRT together with a positive impact on the patient's menopausal related symptoms. However, longer follow-up and future randomized studies are needed.

Keywords

Cytoplasmic pollen extract; Menopausal symptoms; Breast cancer patients; Quality of life; Non-hormonal therapy

1. Introduction

A woman's fertile period ends with menopause, which implies the cessation of the ovarian function and secretion of female hormones. Estrogen deficiency can cause several menopausal symptoms, such as hot flushes (HFs), night sweats, vaginal dryness, psychological symptoms, and sexual dysfunction [1–5]. HFs are the most common symptom and frequently remain underdiagnosed and undertreated, with a negative impact on the patient's quality of life (QoL) [1, 4]. Currently, the most effective therapy available for the treatment of menopause symptoms is the hormone replacement therapy (HRT) [1, 5–7].

Women with a history of breast cancer (BC), ovarian and uterine cancer, or a family history of BC are also particularly

vulnerable to menopause symptoms due to chemotherapy or hormone therapy drugs used to treat BC [8]. Most of these women choose to take HRT to help to reduce symptoms, even though doctors do not recommend them because of the known link between estrogen levels and BC growth [1, 8, 9]. Therefore, HRT is not indicated in these women and alternative treatments should be considered [10–13]. Hence, anti-estrogens appear as potential treatments in the therapeutic strategy, especially for BC survivors.

Recent studies evaluating non-hormonal treatments and complementary and alternative medicines have provided interesting data [6, 7, 10, 12, 13]. Among them, cytoplasmic pollen extract confirmed its non-estrogenic effect and proved to be effective in decreasing HFs, night sweats, irritability and improving the quality of sleep in menopausal women, with the consequent improvement in QoL [2, 6, 7, 10–12, 14, 15].

Cytoplasmic pollen extract is a standardized Swedish natural product used as an herbal remedy to relieve premenstrual, perimenopausal, and menopausal symptoms [6, 7, 15]. It is believed that acts similarly to selective serotonin reuptake inhibitors (SSRIs) by acting on serotonergic neurons in the central nervous system, which control thermoregulation, mood, and sleep [16].

Cytoplasmic pollen extract (Femal[®]) has been available in Europe since 1999 and contains three active agents: purified pollen extract (GC Fem), a mixture of cytoplasmic pollen and pistil extracts (PI 82) and vitamin E, ingredients which are full of antioxidant enzymes (similar to the superoxide dismutase) and natural non-steroid anti-inflammatories [6, 7, 12, 15]. Pollen and pistils are extracted from members of the family of grass (*Poaceae*) and its cultivation and recollection are done in accordance with the recommendations of the European Medicine Agency [6, 7].

In vitro, Swedish GC Fem showed no inhibition of cytochrome P450 2D6 enzyme E and therefore does not interfere with the metabolism of tamoxifen which is a traditionally drug used to treat HR+ subtypes Luminal A and B cancers [11, 15, 16]. On the other hand, experimental studies determined that the preparation of the pollen extract contained low concentrations of the phytoestrogens daidzin, daidzein, and genistin; hence, the possibility of estrogenic ac-

Menopause Rating Scale (MRS)

Which of the following symptoms apply to you at this time? Please, mark the appropriate box for each symptom. For symptoms that do not apply, please mark 'none'.

Symptoms:	none	mild	moderate	severe	very severe
	Score = 0	1	2	3	4
1. Hot flushes, sweating (episodes of sweating).....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
2. Heart discomfort (unusual awareness of heart beat, heart skipping, heart racing, tightness).....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
3. Sleep problems (difficulty in falling asleep, difficulty in sleeping through, waking up early).....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
4. Depressive mood (feeling down, sad, on the verge of tears, lack of drive, mood swings).....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
5. Irritability (feeling nervous, inner tension, feeling aggressive).....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
6. Anxiety (inner restlessness, feeling panicky).....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
7. Physical and mental exhaustion (general decrease in performance, impaired memory, decrease in concentration, forgetfulness).....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
8. Sexual problems (change in sexual desire, in sexual activity and satisfaction).....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
9. Bladder problems (difficulty in urinating, increased need to urinate, bladder incontinence).....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
10. Dryness of vagina (sensation of dryness or burning in the vagina, difficulty with sexual intercourse).....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
11. Joint and muscular discomfort (pain in the joints, rheumatoid complaints).....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Fig. 1. Menopause Rating Scale (MRS).

tivity can be excluded. Additionally, the product showed no contraindication in patients with various allergies because the allergens that are present in the pollen are completely eliminated during the extraction process [7, 12, 15].

Base on this facts, cytoplasmic pollen extract became of particular interest among patients with hormone-sensitive cancers, as they have limited options and safety concerns with the conventional methods used to address such symptoms [16]. Although several studies have demonstrated the efficacy of cytoplasmic pollen extract in menopausal women [2, 3, 6, 7, 12, 15], in BC menopausal women only few studies reported its effectiveness [10, 11].

In this case series study, we aimed to evaluate the efficacy and tolerability of a cytoplasmic pollen extract on menopausal symptoms in BC (HR+) women on adjuvant treatment, over a period of 3 months.

2. Materials and methods

This was a single centre analysis of symptomatic menopausal women with BC on adjuvant hormonal treatment. Twelve women with hormone receptor-positive (HR+), eight with Luminal A and four with Luminal B cancers, with a median age of 47 years (range 37-53 years) were consecutively included in the study (not selected) and received a non-hormonal treatment with cytoplasmic pollen extract (1 capsule/day = 320 mg pollen extract), for 3 months. Participants took the drug in the morning and menopause symptomatology was monitored through the Menopause Rating Scale (MRS) at the beginning of the treatment (T0) and at 90 days (T3). MRS was distributed in Italian and a back translation process was carried out. Adverse events (AEs) were also monitored every month by a phone call

and by personal visit at T3. Tolerability was evaluated by the European Organization for Research and Treatment of Cancer (EORTC) score (Common Toxicity Criteria). The study was conducted using descriptive statistics (frequencies and percentages).

MRS is a formally validated scale according to the requirements for QoL instruments [17] and a valuable tool used worldwide for assessing health related QoL of women in the menopausal transition. It consists of a list of 11 items (symptoms or complaints) with a severity expressed on five-point scale (0, none; 1, mild; 2, moderate; 3, severe; and 4, very severe) (Fig. 1). These items are reported in three dimensions: somato-vegetative dimension, which includes four symptoms: HFs/sweating, cardiac symptoms (e.g., palpitations), sleeping disorders, joint and muscular complaints (from 0 to 16 scoring points); psychological dimension with also four symptoms: depression, irritability, anxiety, physical and mental exhaustion (from 0 to 16 points) and urogenital dimension with three symptoms: sexual problems, urinary complaints, vaginal dryness (from 0 to 12 points).

Individual minimal/maximal scores (from 0 - asymptomatic to 44 - the highest degree) vary between the three dimensions depending on the number of complaints allocated to each dimension of symptoms [18].

3. Results

Here are described 12 cases of patients with BC (HR+) on adjuvant treatment who completed the MRS with the personal appreciation of the menopause symptoms over time (from T0 to T3) (Table 1). All of them were Italian residents. No missing data were reported during study treatment.

Regarding the somato-vegetative dimension, most cases scored the severity of the symptomatology (HFs, cardiac symptoms, sleep problems and joint and muscular discomfort) between 2 (moderate) and 4 (very severe) at T0. An improvement was observed by reducing the severity (given by the score 2 to 4), in all symptoms from T0 to T3, but especially in HFs. Only case 7 got worse in cardiac symptoms (scoring the symptomatology from moderate to severe). On the other hand, the psychological dimension showed less severity from T0 to T3 in irritability and in anxiety. Again, as in the somato-vegetative dimension, only in case 7 increased the level of anxiety (scored from mild to moderate). However, the physical and mental exhaustion showed an increase of severity at T3 in comparison with T0 in case 2 (from moderate to severe), case 3 (from mild to moderate) and case 4 (from none to moderate). Regarding the depressive mood, most cases expressed no changes in severity between T0 and T3. In the case of the urogenital dimension, all symptoms were accompanied by a slight decrease in severity from T0 to T3: sexual problems (cases 2, 6 and 8) and dryness of vagina (cases 4, 5 and 6). Regarding bladder problems, most cases reported having no symptoms in both T0 and T3. Only case 9 did not notice any type of change in any symptoms.

Table 1. Menopause symptomatology for each case at T0 and T3 according to MRS.

	1. Hot flushes		2. Cardiac symptoms		3. Sleep problems		4. Depressive mood		5. Irritability		6. Anxiety		7. Physical and mental exhaustion		8. Sexual problems		9. Bladder problems		10. Dryness of vagina		11. Joint and muscular discomfort	
	T0	T3	T0	T3	T0	T3	T0	T3	T0	T3	T0	T3	T0	T3	T0	T3	T0	T3	T0	T3	T0	T3
Case 1	3	1	2	1	2	2	2	2	3	1	3	2	4	1	3	3	2	2	3	3	2	1
Case 2	4	2	0	0	4	4	4	3	3	1	3	2	2	3	3	2	0	0	2	2	1	1
Case 3	2	1	2	1	3	3	3	3	3	2	1	1	1	2	4	4	0	0	4	4	4	3
Case 4	3	2	3	1	3	1	1	1	4	3	2	1	0	2	3	3	2	1	3	2	4	4
Case 5	4	1	4	2	4	3	3	2	2	1	3	2	1	1	1	1	0	0	2	1	3	3
Case 6	3	0	4	3	2	2	0	0	1	1	3	0	1	1	3	0	0	0	3	2	3	2
Case 7	2	1	2	3	0	0	1	1	4	3	1	2	0	0	2	2	0	0	0	0	2	1
Case 8	4	4	3	3	3	1	0	0	4	3	0	0	3	3	4	2	0	0	4	4	3	3
Case 9	3	3	1	1	2	2	1	1	2	2	3	3	2	2	3	3	3	3	4	4	2	2
Case 10	3	1	1	1	3	1	0	0	0	0	0	0	1	1	2	2	0	0	0	0	4	3
Case 11	4	4	0	1	3	3	1	1	0	0	3	3	3	3	3	3	0	0	2	2	3	3
Case 12	3	1	2	1	2	1	3	1	3	1	2	1	2	1	2	2	1	1	2	2	2	1

MRS, Menopause Rating Scale; T0, at the beginning of the treatment; T3, at 90 days. Score: 0 = none; 1 = mild; 2 = moderate; 3 = severe; 4 = very severe

Fig. 2 shows the changes in menopause symptomatology from T0 to T3 grouped into score 0-1 (none or mild symptoms) and score 2+ (moderate to very severe symptoms).

Finally, tolerance of cytoplasmic pollen extract was excellent. No treatment-related side effect was reported among all cases.

4. Discussion

Menopausal symptoms are occasionally disabling symptoms that affect QoL. Currently HRT is the most effective treatment; however, it is not an option for menopausal women with BC or history of BC. Almost in two-thirds of BC cases, the tumour is hormone-sensitive and non-hormonal therapy is needed to treat menopausal symptoms. Furthermore, BC treatment, such as chemotherapy or estrogen-ablating therapies, exacerbate the frequency and the severity of HFs [1, 10, 19]. This study provides an evidence of the effectiveness and tolerance of cytoplasmic pollen extract, as a non-hormonal therapy, to treat menopausal symptoms in BC (HR+) women with post-menopausal status after 3 months of treatment.

Hot flushes are the most common health problem in menopausal women and the leading cause of disturbance of sleep pattern and depressive symptoms (mainly anxiety and irritability) in this demographic group. The frequency of these symptoms can disable and affect women's psychological health, well-being or social life in the short and long-term. Therefore, a decrease in the intensity and the frequency of HFs may lead to ameliorate other menopause-related complaints associated with both somato-vegetative and psychological symptoms [1, 13]. Several studies have addressed an important role of non-hormonal treatments in menopause-related symptoms. A randomized double-blind placebo-controlled study a significant reduction in HFs (65%) with a specific cytoplasmic pollen extract compared with placebo (38%) in 64 menopausal women after 3 months. There was

also an improvement in tiredness, dizziness, mood, libido, headache, irritability, mood swings, and sensitiveness with the non-hormonal therapy in comparison with baseline [7]. An open study conducted in 417 menopausal women treated with non-hormonal therapy for 3 months showed a reduction in the frequency of HFs (65%), sweating and perspiration (66%), irritability (54%), and fatigue (51%) [6]. In another study conducted in 80 women, standardized pollen extract was associated with an improvement in perimenopausal symptoms such as HFs and mood swings [20]. A randomized placebo-controlled study conducted in 45 women treated with either non-hormonal therapy or with estrogen/progestin therapy or placebo for 6 months confirmed efficacy in reducing the intensity of the neurovegetative symptoms of menopause [15]. A recent prospective observational study performed in 45 women receiving non-hormonal therapy for 12 weeks, HFs were reduced by 48.5%, sleep disturbances by 50.1%, depressive mood by 51.2%, irritability by 47.9% and fatigue by 47.8% [21]. The lack of estrogenic activity makes it a safe non-hormonal option for those menopausal women who cannot undergo HRT [2, 6, 7, 10, 12, 15]. In our study, few changes in urogenital and psychological symptoms were observed over time. Nevertheless, HFs, cardiac symptoms, sleep problems and joint and muscular discomfort showed great improvement in BC (HR+) women after 3 months of treatment (T3) with cytoplasmic pollen extract compared to the start of therapy (T0). These data indicated that cytoplasmic pollen extract can be an effective non-hormonal alternative for alleviating menopausal symptoms in women with BC.

The safety profile and tolerability observed in our study were similar to other studies performed in both menopausal and BC menopausal women receiving therapy with GC FEM, PI 82 and vitamin E [2, 6, 7, 10-12, 15]. In all these studies, the participants reported a very good tolerance of PI 82-GC FEM with only minor and clinically insignificant adverse

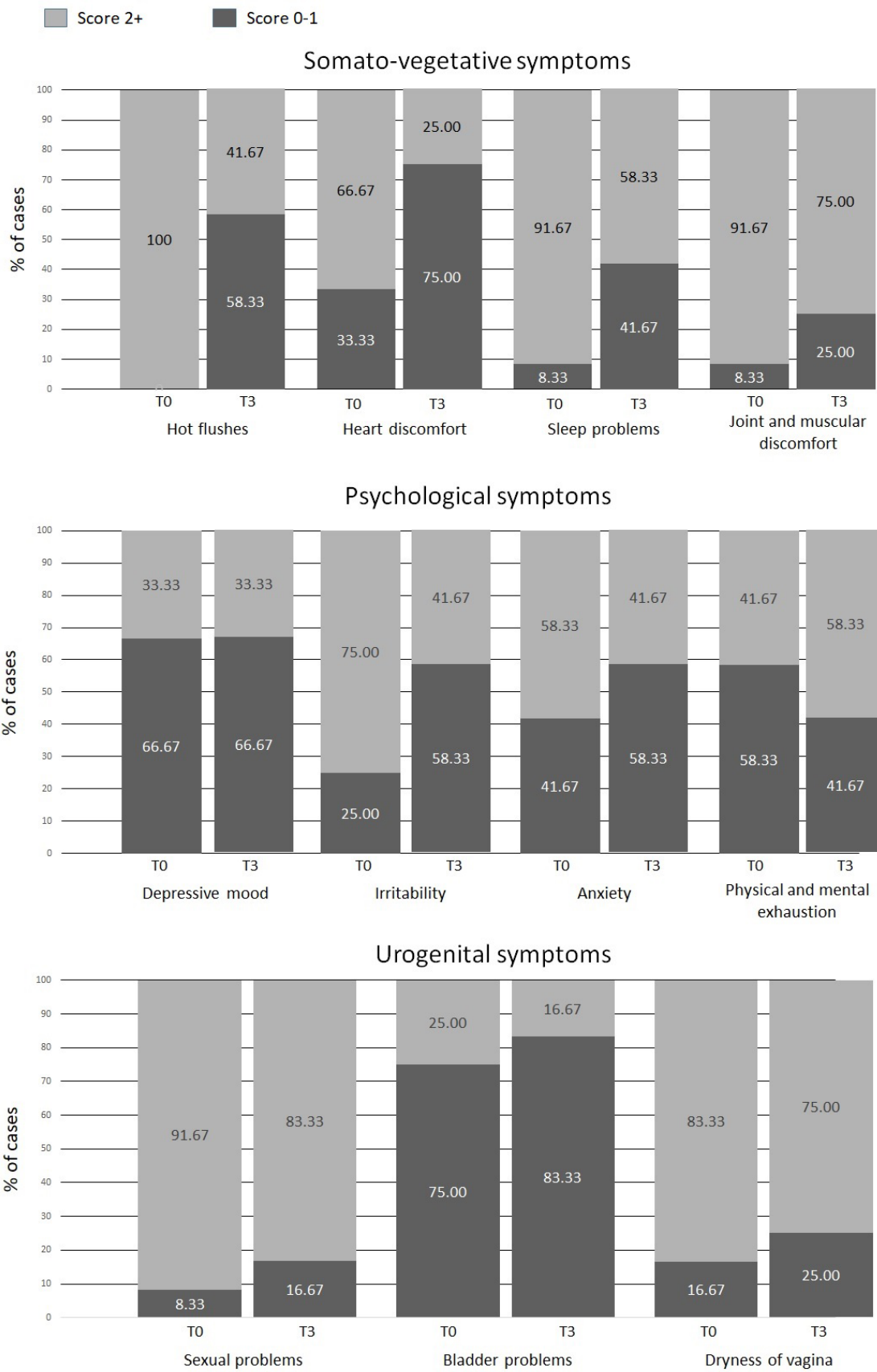


Fig. 2. Changes in menopause symptomatology from T0 to T3 grouped into score 0-1 (none or mild symptoms) and score 2+ (moderate to very severe symptoms).

events. Regarding our study, no treatment-related side effects were reported during treatment, suggesting that cytoplasmic pollen extract might be an advantageous and safe treatment option to HRT.

The results of our study should be interpreted in the context of its limitations. One of the weaknesses found relies on the small sample size and the observational, case series design, not allowing us to obtain statistical results. The absence of a comparison group and the lack of long-term follow up were other weaknesses. Despite these limitations, our study provide some evidence of efficacy and safety of cytoplasmic pollen extract in BC (HR+) menopausal women, which is of value given the small number of studies conducted in this field.

5. Conclusions

The results of this observational case series study suggest that cytoplasmic pollen extract may be safe and effective therapy in women with contraindications to HRT. However, longer follow up and future randomized studies are needed to evaluate differences between cytoplasmic pollen extract and other therapies, in order to improve the QoL of menopausal women with BC (HR+) or a history of BC.

Author contributions

AI designed the research study. AI, PD, AZ and MM performed the research. AI analysed the data and wrote the manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Hereby we confirm that procedures involving experiments of human subjects were done in accordance with the ethical standards of the Committee on Human experimentations of the institution in which the experiments were done or in accordance with the Helsinki Declaration.

All patients gave written informed consent.

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Conflict of interest

The authors declare no conflict of interest.

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