

# Purified and Specific Cytoplasmic Pollen Extract for the treatment of vasomotor menopausal symptoms: a review

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## ABSTRACT

**Background and purpose:** In the developed world, vasomotor disorders are the most common menopausal symptoms and hormone replacement therapy (HRT) is the most effective remedy. This review aims to show that the Purified and Specific Cytoplasmic Pollen Extract is an effective and safe alternative in the treatment of vasomotor symptoms for women who cannot or do not want to take hormones.

**Methods:** A review was performed searching articles published on PubMed.

**Results:** It has been shown in several *in vitro* and *in vivo* studies that Purified and Specific Cytoplasmic Pollen Extract is a safe natural remedy that has no carcinogenic and estrogenic activity. Several trials have demonstrated a statistically significant improvement of vasomotor symptoms (hot flushes and sweats) in women who took the product for three months.

**Conclusions:** Purified and Specific Cytoplasmic Pollen Extract has proven to be an effective and safe non-hormonal alternative for reducing vasomotor symptoms in women who do not wish to take hormones or for whom HRT is contraindicated, as breast cancer survivors.

## KEYWORDS

Pollen extract, vasomotor symptoms, breast cancer, sleep disorders.

## Introduction

The average age of menopause is 51 years and women's life expectancy exceed 80 years; this means that a woman could live two thirds of her life in menopause. This physiological phase of life is characterized by a decline in estrogen and progesterone levels, which lead to the onset of typical symptoms, such as vasomotor symptoms (hot flushes and night sweats), insomnia, vaginal atrophy, urinary disorders, sexual dysfunction, poor memory, depression and anxiety <sup>[1]</sup>. In the developed world, vasomotor disorders are the most common menopausal symptoms, occurring in approximately 60-80% of women <sup>[2]</sup>. They seem to be caused by the alteration of the thermoregulatory center, following the decline in estrogen blood levels, but they are a multifactorial phenomenon conditioned by genetics, lifestyle and psychosocial characteristics <sup>[3,4]</sup>.

It is well-known that the most effective therapy for vasomotor symptoms is hormone replacement therapy (HRT). However, there are women who cannot or do not want to take hormones. In breast cancer survivors HRT is generally not advised <sup>[5]</sup>. The goal of adjuvant endocrine therapy in breast cancer patients is to reduce the availability of estrogen in cancer cells, but, on the other hand, this hormonal deprivation leads to a greater intensity and duration of menopausal symptoms, especially in younger patients <sup>[6]</sup>. Approximately 30-40% of breast cancer patients consider stopping or actually cease adjuvant endocrine therapy because of uncontrolled menopausal symptoms <sup>[7]</sup>. For these patients, as well as for those women

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who prefer not to take hormonal therapies, it is clearly necessary to resort to non-hormonal alternatives, which could be pharmacological, such as antidepressants, anti-hypertensives, vitamin E or non-pharmacological, such as black cohosh, pollen extracts, lifestyle change, hypnosis, breathing techniques, acupuncture and yoga. Choosing among the various non-hormonal treatments is not that simple. A US online survey completed by 781 midlife women revealed that 73% of them do not feel well informed about therapeutic possibilities, in particular about herbal products, and 58% of them reported having concerns about these remedies <sup>[8]</sup>.

This review focuses on Purified and Specific Cytoplasmic Pollen Extract and aims to highlight how this herbal product has proven to be safe and effective for the treatment of vasomotor symptoms.

## Materials and methods

We searched PubMed using the following keywords: "pollen extract and menopausal symptoms"; "pollen extract and breast

cancer”; “pollen extract and vasomotor symptoms”. Few results were obtained and therefore all were analyzed. Original papers selected for inclusion were independently reviewed by the authors. Only the publications written in English were considered.

## Discussion

### Composition and mechanism of action

Pollen is the male gametophyte of the flower and has long been used for therapeutic purposes by various civilizations because it contains many important elements, such as proteins, amino acids, sugar, minerals, vitamins, natural antibiotics, fats. The external shell contains allergens and its function is to protect the genetic material, while the center of the pollen contains the cytoplasm<sup>[9]</sup>. Moreover, it cannot be damaged by gastric acid digestions<sup>[10]</sup>.

Pollen extraction has its origin in the 1940s, when the Swedish gynecologist Gosta Carlsson discovered how to obtain only the internal part of the pollen grain cytoplasm. During this process, the external shell of the pollen is completely removed, thus minimizing the risk of allergic reactions and the extract is mixed in a standardized formulation: tablets which always contain 40 mg of pollen extract GCFem and 120 mg of pollen/pistil extract PI82, no less than 10 mg of amino acids and 5 mg of vitamin E. The recommended daily dose is 2 tablets, which corresponds to a total dose of pollen extract of 320 mg<sup>[11]</sup>.

Purified and Specific Cytoplasmic Pollen Extract acts similarly to selective serotonin reuptake inhibitors (SSRI), without the known adverse effects of these drugs. Moreover, it contains tryptophan, which is known to be a precursor of serotonin.

This herbal preparation seems to maintain the availability of serotonin in hypothalamic serotonergic neurons and this could explain its efficacy in controlling thermoregulation, sleep and mood in menopausal women<sup>[4]</sup>.

Several *in vitro* and *in vivo* trials have evaluated the efficacy and safety of Purified and Specific Cytoplasmic Pollen Extract. Hellstrom *et al.*<sup>[12]</sup> demonstrated that Purified and Specific Cytoplasmic Pollen Extract shows no trace of phytoestrogens and no estrogenic activity, with no *in vivo* uterotrophic effect, compared with ethinylestradiol. In particular, they examined the concentration of 6 common isoflavonoid phytoestrogens in the Purified and Specific Cytoplasmic Pollen Extract with the HPLC method, finding a subeffective minimal amount of daidzin, daidzein and genistin and no trace of genistein, formononetin or biochanin A.

Seeger *et al.*<sup>[13]</sup> tried to determine if there may exist a small breast cancer risk by stimulating other steroidal receptors than nuclear ER. Receptor membrane-initiated actions of Purified and Specific Cytoplasmic Pollen Extract in comparison to estradiol (E2) and growth factors (IGF, FGF, EGF) were analyzed in two different breast epithelial cancer cells (MCF7 and TD47) transfected with PGRMC1. Hormone receptor positive breast cancer cells responded to E2 and growth factors by an increased proliferation rate and a downregulation of apoptosis, while Purified and Specific Cytoplasmic Pollen Extract was neutral on the transfected cell lines or not those not transfected

with PGRMC1 in terms of cell proliferation and cell apoptosis, also in combination with E2 or growth factors. The authors concluded that the reduction of vasomotor symptoms reported by postmenopausal women treated with Purified and Specific Cytoplasmic Pollen Extract may not be mediated by estrogen or estrogen-like pathways<sup>[3]</sup>.

In a randomized, double-blind, placebo-controlled, parallel trial performed on 64 menopausal women, Winther *et al.*<sup>[14]</sup> demonstrated that there were no differences between hormone levels of women taking Purified and Specific Cytoplasmic Pollen Extract in comparison to those taking placebo, as both showed high levels of FSH, low levels of estrogen and no changes in the level of SHBG or testosterone<sup>[4]</sup>.

Subsequently, Goldstein *et al.*<sup>[15]</sup> evaluated the potential interaction of Purified and Specific Cytoplasmic Pollen Extract with tamoxifen through the inhibition of the CYP2D6 enzyme at high concentrations in pooled liver microsomes with quinidine as a control. No inhibition of CYP2D6 was found with Purified and Specific Cytoplasmic Pollen Extract<sup>[5]</sup>. This data has a primary clinical importance because other non-hormonal treatments, such as SSRIs, strongly inhibit CYP2D6 enzyme, thus leading to a potential significant reduction of the efficacy of tamoxifen in breast cancer survivors<sup>[16]</sup>.

Moreover, studies regarding oral toxicity and potential mutagenic activity of Purified and Specific Cytoplasmic Pollen Extract have been conducted, demonstrating that the compound is safe and non-toxic when a single high dose is administered to mice, and that it has no carcinogenic potential<sup>[17-19]</sup>.

To further improve the treatment of sleep disorders related to the menopause, magnesium and melatonin have been added to Purified and Specific Cytoplasmic Pollen Extract in a more recent formulation (melatonin 1 mg and magnesium 56.25 mg per capsule in addition to the original daily dose of pollen extract and vitamin E).

The mechanisms behind menopausal insomnia are multifactorial and related to hormonal changes, other menopausal symptoms and mood disorders. Progesterone has an anxiolytic and sedative activity and it appears to stimulate benzodiazepine receptors. Estrogens seem to decrease sleep latency and the number of awakenings. During the menopausal transition, the reduction of melatonin and the change in the circadian rhythm also seems to affect sleep regulation<sup>[20,21]</sup>. Treatment with exogenous melatonin has a mild hypnotic effect and does not provoke somnolence in the morning<sup>[22]</sup>. The Italian recommendations for the treatment of insomnia over the age of 55 in clinical practice suggest melatonin as the first line approach<sup>[23]</sup>.

Melatonin administration in postmenopausal women suffering from insomnia has shown a significant improvement in sleep quality compared to placebo<sup>[24]</sup>. Magnesium is a structural component of organic molecules and a cofactor in hundreds of enzymatic reactions involved in various processes. It contributes to the reduction of fatigue and to the proper functioning of the nervous system, acting as an agonist of GABA receptors and having a relaxing action. In a double-blind, placebo-controlled trial, dietary magnesium supplementation compared to placebo, lead to a significant increase in sleep time and quality, concentration of serum renin and melatonin and a decrease of ISI scores (Insomnia Severity Index), sleep onset latency and

serum cortisol concentration [25]. For these reasons, the combination of Purified and Specific Cytoplasmic Pollen Extract, melatonin and magnesium should be useful to control sleep disturbances in postmenopausal women, when they are the dominant complaint.

### Efficacy of Purified and Specific Cytoplasmic Pollen Extract on menopausal symptoms

The efficacy of Purified and Specific Cytoplasmic Pollen Extract in the treatment of menopausal symptoms has been demonstrated in several clinical trials. Most of them have been conducted comparing Purified and Specific Cytoplasmic Pollen Extract to placebo, showing a significant decrease in hot flushes, insomnia, depression, irritability and fatigue after 12 weeks of treatment, with minimal side effects [14,26-29].

Winther *et al.* [14] trial showed that 65% of women treated with Purified and Specific Cytoplasmic Pollen Extract experienced a decrease in hot flashes compared with only 38% of the placebo group. In a trial of 417 menopausal women taking two Femal® tablets per day for 84 days, a significant effectiveness of Purified and Specific Cytoplasmic Pollen Extract was observed on vasomotor symptoms (hot flushes and sweats), and a significant improvement in the quality of life, irritability and fatigue, as assessed by a questionnaire and visual analogical scales (VAS) [26]. A prospective, open, observational and multicentre study was performed on 104 menopausal women, who received 2 tablets of Purified and Specific Cytoplasmic Pollen Extract per day over 3 months. Using the menopausal rating scale (MRS), a significant decrease of many menopausal symptoms such as hot flashes, sleep disturbance, depression, fatigue and vaginal dryness was observed after 12 weeks ( $p < 0.0001$ ) [27]. In a recent publication aimed at observing the effects of Purified and Specific Cytoplasmic Pollen Extract and soy isoflavones on menopausal complaints, particularly on sleep disorders, 3 groups of women were treated for 6 months: 57 treated with Purified and Specific Cytoplasmic Pollen Extract, 60 receiving isoflavones and 47 receiving no treatment. Improvement of global sleep quality was significantly more evident in the Purified and Specific Cytoplasmic Pollen Extract treated group compared to isoflavones group at both three (-24.7% versus -9.3%,  $p < 0.001$ ) and six (-52.9% vs -4.0%;  $p < 0.001$ ) months [28].

Lello *et al.* [29] evaluated 108 peri- and post-menopausal women in a multicentre prospective observational Study. Demonstrating a significant improvement in hot flushes and night sweats after 3 months of treatment with Purified and Specific Cytoplasmic Pollen Extract.

Preliminary data from a double blind, randomized, prospective trial conducted in Italy with the purpose of evaluating the efficacy and tolerability of Purified and Specific Cytoplasmic Pollen Extract in the treatment of vasomotor symptoms in breast cancer survivors have been presented at the International Society of Gynecological Endocrinology Congress held in Florence in May 2022. The study population consisted of 20 women under placebo compared with 19 women taking Purified and Specific Cytoplasmic Pollen Extract. The frequency and severity of vasomotor symptoms were analyzed by daily diary and by the MRS. Furthermore, the PSQI scale (Pittsburgh Sleep Quality Index), 6 VAS scales for hot flushes and sweat-

ing, irritability, fatigue, sleep and quality of life and the ELIA questionnaire evaluating hot flushes frequency, intensity, onset, sweating discomfort and intensity, irritability, tiredness, sleep and quality of life were employed. A statistically significant reduction was found in the number of hot flushes and hot flush intensity, sweat discomfort, irritability and fatigue in VAS scale in the Purified and Specific Cytoplasmic Pollen Extract group after 3 months of therapy versus placebo group. Total MRS scores were significantly improved in both groups after 3 months of treatment, but in the Purified and Specific Cytoplasmic Pollen Extract group the significant improvement was observed already after the first month [30].

### Conclusions

Purified and Specific Cytoplasmic Pollen Extract has proven to be an effective non-hormonal alternative for reducing vasomotor symptoms in women who do not wish to take hormones or for whom HRT is contraindicated, as breast cancer survivors. In fact, it seems that Purified and Specific Cytoplasmic Pollen Extract is safe for these women and do not increase the risk of breast cancer, although further *in vivo* studies on breast cancer survivors are needed. Moreover, Purified and Specific Cytoplasmic Pollen Extract does not interfere with CYP450, being a safe option also for women under tamoxifen. The combination of Purified and Specific Cytoplasmic Pollen Extract, melatonin and magnesium seems to be an effective option when sleep disturbances are the main menopausal symptom. There is need of further studies to evaluate the efficacy of this formulation.

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