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A prospective, multicenter, randomized, double-blind placebo-controlled trial on purified and specific Cytoplasmic pollen extract for hot flashes in breast cancer survivors

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ABSTRACT

Objective: evaluate the efficacy and tolerability of PureCyTonin against hot flashes (HF) in breast cancer survivors (BCS).

Methods: a prospective, multicenter, randomized, double-blind placebo-controlled trial was conducted in Italy.

Interventions: administration of PureCyTonin or placebo, for 3 months. Effectiveness was investigated through the compilation of a daily diary for HF and of validated questionnaires (Menopause Rating Scale (MRS), Pittsburgh Sleep Quality Index (PSQI), Visual Analogical Scales (VAS) for HF, sweating, irritability, fatigue, sleep, quality of life), carried out before starting the treatment (T0), after 1 month (T1) and after 3 months (T2). Any side effects and HF diary were recorded at each visit.

Results: 19 women were randomized to receive PureCyTonin and 20 to placebo. At T2 compared to T0, in the PureCyTonin group, we found a reduction in the number of HF ($p=0.02$) measured by daily diary. An improvement in the subjective perception of women regarding HF intensity ($p=0.04$), sweat nuisance ($p=0.02$), irritability ($p=0.03$) and fatigue ($p=0.04$) was observed through VAS scale measurement at T2 compared to T0.The total MRS score was significantly better in the PureCyTonin group at T1 ($p=0.03$) compared to T0.

Conclusions: PureCyTonin significantly reduces HF number after 3 months of therapy in BCS and it is well-tolerated.

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Pollen extract; vasomotor symptoms; hot flashes; breast cancer survivors; randomized controlled trial

Introduction

Early diagnosis and progress in breast cancer (BC) treatments resulted in a significant increase in survival, while treatment-related toxicity can adversely affect patients' quality of life (QoL) [1]. Vasomotor symptoms, such as hot flashes (HF) or night sweats, are frequent and severe among women in iatrogenic or spontaneous menopause, especially after chemotherapy or endocrine therapy required for cancer control [2]. However, the use of hormone replacement therapy (HRT) is generally not advised for women with a previous history of BC [3], and alternative options are needed for HF [4,5].

Non-hormonal treatments include drug therapies (antidepressants belonging to the classes of selective serotonin and norepinephrine reuptake inhibitors (SSRI) and of selective serotonin-norepinephrine reuptake inhibitors (SNRI), clonidine, anticonvulsants, oxybutynin, neurokinin receptor antagonists) and non-drug therapies, including black cohosh, Purified and specific Cytoplasmic pollen Extract, acupuncture, stellate ganglion block, yoga, cognitive-behavioral and relaxation techniques [4–7].

Among non-hormonal drugs, the SSRI antidepressant paroxetine [8] and the neurokinin 3 receptor antagonist fezolinetant [9] are currently the only FDA approved treatment for HF.

However, in breast cancer survivors (BCS) treated with tamoxifen, a pharmacological interference of antidepressants has been reported, since they can inhibit CYP2D6 enzyme, with subsequent reduction of the active metabolite of tamoxifen [4,5].

Among the alternative options, the Purified and Specific Cytoplasmic Pollen Extract (PureCyTonin) seems promising. It contains a pure pollen extract (GC Fem), a combined pollen and pistil extract (PI 82) and vitamine E [10,11]. It acts on HF similarly to SSRI antidepressants, but it does not interfere with the cytochrome involved in tamoxifen's metabolism [5,10–14]. Furthermore, the production technology allows the elimination of potential allergens ensuring patient safety, without any contraindications of its use in patients with pollen allergy [5].

The pollen extracts come from selected plants belonging to the Gramineae family and Pinaceae family and are harvested separately using a standardized method. PureCyTonin is a natural non-hormonal extract, and it contains proteins, amino acids, sugar, minerals, vitamins, and fats [10,12]. PureCyTonin seems to

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act through the inhibition of the synaptic absorption of serotonin in a dose-dependent manner and it has strong antioxidant properties [5,10,11,13]. A detailed study of the phytoestrogen composition analysis revealed no traces of genistein, formononetin, or biochanin A, and very minimal sub-effective concentrations of daidzein and genistein in these pollen extracts, thus ruling out any estrogenic action of pollen extracts [15]. In the same stud, PureCyTonin does not cause any uterine growth in experimental models in immature female rats, showing no estrogenic effect [15]. The lack of estrogenic effects, also confirmed in another *in vitro* studio showing a neutral effect in cell lines [16], makes this preparation of particular interest for BCS.

In literature, it is shown that PureCyTonin is effective in the treatment of vasomotor symptoms, however most of the data come from studies performed in healthy women [17–19]. In the double-blind, placebo-controlled trial by Winther et al. no evidence of abnormal uterine bleeding or change in circulating sex hormone levels was observed before and after the study period, confirming no estrogenic activity [17].

To our knowledge, at the moment, only a case series of 12 patients was published employing PureCyTonin in BCS [20].

The aim of our study is to demonstrate the efficacy of PureCyTonin in reducing the frequency of HF in a prospective, multicenter, randomized, double-blind, placebo-controlled trial on a population of BCS and to validate its safety and tolerance, through objective evaluations by validated questionnaires and scales.

Methods

Study design

A prospective, multicenter, randomized, double-blind placebo-controlled trial was performed in Italy.

Women eligible for this study had previous BC, spontaneous or iatrogenic menopause, or were premenopausal with hormone-suppressed ovarian function. To be randomized they had to experience severe vasomotor symptoms (at least 20 HF per week). Anti-estrogen or aromatase inhibitors were allowed if they were started at least 2 months before study entry. Exclusion criteria were the treatments with antidepressants started less than 4 weeks before the enrollment.

Enrolled patients were randomly assigned to PureCyTonin 320 mg/day (2 tablets/day) or placebo (2 tablets/day) for 3 months (double-blind study). Randomization codes have been produced by IBISMed, a clinical research organization, independent from the study sponsor. To each eligible subject a consecutive randomization number was assigned, to keep the subject's identity confidential. Written informed consent was collected before randomization.

Evaluations

The evaluations were performed before starting the treatment (T0), after 1 month of therapy (T1) and after 3 months of therapy (T2). In each visit the following parameters were evaluated:

1. frequency and severity of vasomotor symptoms by daily collection (HF diary). This well-validated diary, originally developed by the North Central Cancer Treatment Group, has been used in several controlled trials with the same purpose [21]. Patients classified the severity of HF as mild, moderate, severe or extremely severe.
2. menopausal symptoms using the Menopause Rating Scale (MRS) [22]. It includes investigation of HF, sweating, heartbeat anormalities, sleep disturbances, decreased mood, irritability, anxiety, physical and mental breakdown, sexual problems, urinary problems, dryness of the vagina, and joint and muscular complaints. Each symptom can be rated to 5-point. The total MRS score goes from 0 to 44 points and is then subdivided into a somato-vegetative domain (items 1, 2, 3 and 11), a psychological domain (items 4, 5, 6 and 7) and a urogenital domain (items 8, 9 and 10).
3. sleep quality using the Pittsburgh Sleep Quality Index (PSQI) scale [23]. Nowadays the PSQI is the only standardized clinical instrument to assess the sleep quality. The PSQI is a 19-item questionnaire. It evaluates the subjective quality of sleep, sleep latency, sleep duration, habitual sleep efficacy, sleep disturbances, use of hypnotic drugs and disturbances during the day. The overall score ranges from 0 to 21. If it is less or equal to 5, it means good sleep quality, a score greater than 5 indicates poor sleep quality.
4. Visual Analogical Scales (VAS) for 6 menopausal parameters (HF and sweating, irritability, fatigue, sleep, QoL) [24]. First published around 1920, the VAS scale finds its origin in some visual-analogical scales developed in the field of psychology to measure well-being. It is one of the best-known one-dimensional measures for pain intensity. In our study we employed the VAS scale to explore the discomfort felt by the women related to menopausal symptoms (HF frequency, HF intensity, HF nuisance, sweat frequency, sweat intensity, sweat nuisance, irritability, fatigue, sleep, QoL). It corresponds to the visual representation of the amplitude of the symptoms felt and consists of a line 10 cm long, where the left extremity corresponds to 'no symptom', while the right extremity corresponds to 'worst possible symptom'. The patient is asked to draw a sign on the line that represents the level of the disturbance created by the presence of the symptom.
5. side effects have been recorded daily and tolerance was assessed on each visit on a 4-level scale: 1 = excellent tolerance: absence of any undesirable effect; 2 = good: mild and brief symptoms, felt or noticed at the start of the study, then disappeared; 3 = medium: undesirable effect showing only moderate and elusive symptoms or minor symptoms, felt or noticed several times; 4 = poor: undesirable effect showing objectively clear and persistent symptoms. Only clinical outcomes were considered.

Endpoints

The primary endpoint is the effectiveness of PureCyTonin in reducing HF in T0-T2 time frame versus placebo. Secondary endpoints are changes in the frequency of HF sweating, irritability, fatigue, sleep, and QoL in T0-T2 at VAS scale.

Institutional review board statement

The study was approved by the Ethics Committee of the hospital (number of practice CS2/923 approved on 29 September 2018) and was conducted following Helsinki principles. Each patient signed informed consent to receive the treatment and to have their clinical data included in the hospital databases for research analyses.

Statistics

All results have been analyzed using descriptive statistics appropriate to the nature of the variables, based on the intention to treat. Continuous variables are presented with the number of observations, mean and standard deviation, minimum, median and maximum value. Categorical data are presented as frequencies and percentages. The Mann-Whitney U test has been used for continuous variables, and Fisher's exact test for categorical variables. A bilateral significance level of 0.05 will be set for each contrast. Statistical analysis has been performed using IBM-SPSS statistics® Version 28.0.1.1 (15) (New York 10504-1722 United States).

Results

Study population

Thirty-nine women were enrolled from November 2019 until September 2021. Delays and decreases in recruitment occurred, due to the COVID-19 pandemia, which stopped the enrollments for more than 6 months. After that, many patients did not attend the visit in menopausal service, due to the fear of entering the hospital for the COVID −19 pandemia. Twenty women were randomized to placebo, nineteen to PureCyTonin. Median age at enrollment was 51 years. Nine patients dropped out: 8 patients withdrew due to the COVID-19 pandemia, not attending visit in the hospital for fear, just 1 patient withdrew due to minor side effects. The remaining 30 women completed the path. The last questionnaire was registered in December 2021.

The characteristics of the population were comparable in the two groups (Table 1). The mean time since surgery to randomization was 31 months (39 months in the placebo group and 25 in the Pure PureCyTonin group).

Table 1. Characteristics of the study population.

	PureCyTonin ($N=19$)	Placebo ($N=20$)
Menopause age (median, years)	47	47
Pharmacological menopause	12	15
Iatrogenic menopause	1	1
Spontaneous menopause	6	4
BMI (mean, Kg/m2)	25.6	24.3
Use of antidepressant > 4 weeks	1	2
Adjuvant CT	9	7
Adjuvant ET		
Ongoing	16	16
Previous Use	1	2
Never	2	2
Type of ongoing ET		
Tam alone	2	3
Tam + GnRH analogh	5	4
AI alone	3	2
AI + GnRH analogh	6	7

Body Mass Index (BMI); chemotherapy (CT); endocrine therapy (ET); Tamoxifen (Tam); Gonadothropin releasing hormone (GnRH); Aromatase Inhibitor (AI).

HF diary

Before starting the treatments (T0), the mean weekly HF number in the PureCyTonin group was 45.6, while in the placebo group 49.9. At T1 no significant reduction was observed in any of the two groups, compared to T0. At T2, we observed a significant reduction only in the PureCyTonin group (28.6 HF, $p=0.02$), but not in the placebo group (41 HF, $p=0.24$), compared to T0 (Figure 1).

As regards the intensity of symptoms in the HF's diary, no significant differences were observed due to the limited sample size in relation to the four categories in which severity was classified.

Menopause rating scale score

Results of MRS scores are shown in Table 2.

Total MRS score

Before starting the treatments, the mean Total MRS score evaluating altogether menopausal symptoms in somato-vegetative plus psychological plus urogenital spheres, in the PureCyTonin group was 22.63, while in the placebo group 21.4. After one month, at T1, in the PureCyTonin group there was a significant reduction in the total MRS score compared to T0 (15.54; $p=0.03$). In the placebo group this reduction was not noticed. After 3 months, the score was reduced in both groups, compared to T0.

Psychological MRS score

Before starting the treatments, the mean Psychological MRS value, evaluating depression, irritability, anxiety and physical and

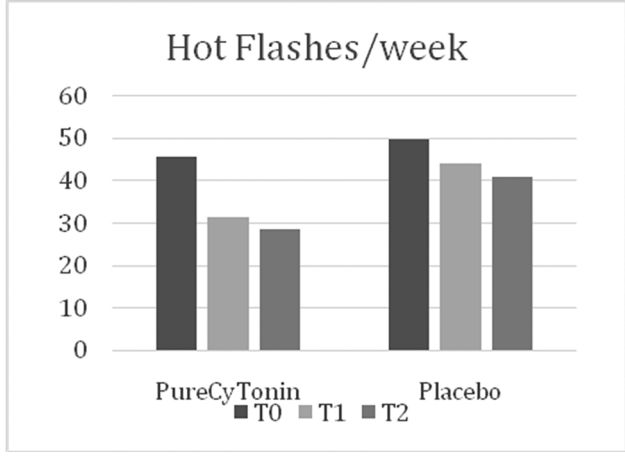

Figure 1. Number of hot flashes per week in PureCytonin and placebo groups at T0, T1 and T2 (TO-T2 in the PureCytonin group $p=0.02$).

Table 2. Menopause rating scale (MRS) results.

	PureCyTonin ($N=19$)			Placebo ($N=20$)		
	T0	T1	T2	T0	T1	T2
Tot MRS score	22.63	15.54 ($p=0.03$)	15.31 ($p=0.03$)	21.4	16.29 ($p=0.09$)	14.59 ($p=0.02$)
SV MRS score	8.42	5.7 ($p=0.09$)	6.15 ($p=0.17$)	6.7	5.7 ($p=0.57$)	4.7 ($p=0.28$)
P MRS score	9.32	6.7 ($p=0.03$)	5.77 ($p=0.005$)	9.6	6.8 ($p=0.005$)	4.7 ($p=0.009$)
U MRS score	4.89	3 ($p=0.26$)	3.38 ($p=0.29$)	5.05	3.73 ($p=0.22$)	3.12 ($p=0.07$)

Total Menopause Rating Scale (Tot MRS); Somato-Vegetative Menopause Rating Scale (SV MRS); Psychological Menopause Rating Scale (P MRS), Urogenital Menopause Rating Scale (U MRS).

mental exhaustion, in the PureCyTonin group was 9.32, while in the placebo group 6.7. At T1 and T2, compared to T0, significant reduction was observed in both groups (5.7, $p = 0.005$ and 4.7, $p = 0.009$ respectively).

Urogenital MRS score

Before starting the treatments, the mean Urogenital MRS value, evaluating sexual problems, urinary problems and vaginal dryness, in the PureCyTonin group was 4.89, while in the placebo group 5.05. At T1 and T2, compared to T0, no significant reduction was observed in any group.

Somato-vegetative MRS score

Before starting the treatments, the mean Somato-vegetative MRS value, evaluating HF, sweating, heart discomfort, sleep problems and arthralgia, in the PureCyTonin group was 8.42, while in the placebo group 6.7. At T1 and T2 no significant reduction, compared to T0, was observed in any group.

Pittsburgh sleep quality index (PSQI) scale

In both groups, we found poor basal quality of sleep (value ≥5) (at T0 mean PSQI scale value in the PureCyTonin group was 9.63, while in the placebo group 8.85). At T1 and T2, compared to T0, no significant reduction was observed in any group.

Visual analogic scale

After 3 months (T2) compared to T0, in the PureCyTonin group there was a reduction in the subjective perception of women regarding HF intensity (7.21 at T0 and 5.38 at T2; $p = 0.04$), sweat nuisance (7.74 at T0 and 5.62 at T2; $p = 0.02$), irritability (6.16 at T0 and 3.77 at T2; $p = 0.03$), and fatigue (6.89 at T0 and 4.62 at T2; $p = 0.03$) expressed through a VAS scale. In both groups, no effect was found on sleep quality.

Side effects and tolerance

Leg pain was registered in one patient assuming PureCyTonin and, for this reason, the patient dropped out of the study. Nobody else felt other kinds of side effects.

In the PureCyTonin group, at T2 tolerance was excellent (score = 1) in 85% of patients, good (score =2) in 8% and modest (score = 3) in 7%.

Discussion

BC is the more frequent cancer among women [25], however, the 5-year relative survival is more than 95% in early stages. The improvement in early detection and treatment led to a massive increase in the diagnosis of early BC and consequentially in the number of BCS.

BCS have to deal with more severe menopausal symptoms compared to healthy women since often undergo pharmacological menopause, and they have few therapeutic options to face them. In particular vasomotor symptoms occur in young women diagnosed with BC: severe HF are a big unsolved problem, that strongly impacts on QoL of BCS [26,27], often determining a discontinuation of adjuvant treatments [2,28]. The use of HRT in BCS is still generally not advised [3]. For these reasons, non-hormonal strategies are needed in BCS. In the last decades this topic has been increasingly addressed [1,4,5,27,29–32].

Among the different alternative options for BCS, PureCytonin can be promising [5,10]. The efficacy of PureCyTonin has been shown in healthy women in different clinical trials [17–19], demonstrating a significant decrease in HF, insomnia, depression, irritability, and fatigue after 3 months of treatment, without side effects.

Winther et al. in 2005 performed a randomized, double-blind, placebo-controlled trial in 64 healthy menopausal women. The women were randomly assigned either to two PureCyTonin tablets or two placebo tablets, for 3 months of treatment. PureCyTonin determined a significant reduction by 65% in HF (versus 38% in the placebo group, $p < 0.006$) [17]. Elia et al. in 2008 carried out a trial with 417 menopausal women, showing a significant role of PureCyTonin on HF and sweats treatment, with a subsequent significant improvement in the QoL, irritability and fatigue [33]. In 2021 Lello et al. on behalf of the Italian Society of Menopause (SIM) and Italian Society of Gynecology of the Third Age of Women (SIGiTE), conducted a trial in which 108 women were recruited, evaluating them at baseline and after 3 months of PureCyTonin treatment, showing a significant improvement of HF and night sweats [18].

As regards women with a previous history of BC, at our knowledge, only a case series of 12 BCS was published in 2021 by Iop et al. showing a reduction in HFs, cardiac symptoms, irritability and anxiety [20].

Our study is the first double-blind randomized placebo-controlled trial specifically addresses to BCS. After 3 months, we found a significant reduction of HF number measured through the HF's diary in the PureCyTonin group compared to baseline. In women receiving PureCyTonin for 3 months, a significant improvement in the subjective perception regarding menopausal symptoms' impact was also observed through the VAS scale for HF intensity, sweat nuisance, irritability, and fatigue.

Already Fait et al. in 2019 performing a prospective, open, observational, and multicenter study in 104 menopausal healthy women, demonstrated, through MRS score, a significant decrease in HF and improvement in sleep disturbances, depression, and fatigue after 12 weeks [19]. In our population the total MRS score was significantly better in PureCyTonin after 1 month. Psychological well-being, explored through MRS score, was improved both by PureCyTonin and placebo after 3 months. This finding could be explored and may be explained with the well-known placebo-effect [34].

Concerning sleep disturbances, in BCS symptoms are worse than in healthy menopausal women; poor sleep quality afflicts many BCS, with a consequent negative impact on QoL [1,2,32,35].

A recent publication of De Franciscis et al. in 2020 compared PureCyTonin and soy isoflavones on menopausal complaints for 6 months (57 healthy women treated with pollen extracts, 60 receiving isoflavones and 47 not receiving any therapy). An improvement of global sleep quality was shown in the PureCyTonin group, compared to the isoflavones group [36]. In contrast, we did not find any kind of improvement on sleep quality neither in the Pittsburgh Sleep Quality Index (PSQI) scale, nor in the VAS scale. Other investigations are needed on this topic, given the inconsistency of the results in the literature about it. The association of PureCyTonin with melatonin and magnesium in a new formulation can be promising for BCS with sleep disturbances. In a randomized, double-blind, placebo-controlled study on 95 BCS, half of the participants reported poor sleep in the month prior to enrollment and the administration of melatonin for 4 months determined a significant

improvement in subjective sleep quality, without any significant adverse effects [37]. A supplementation with 400 or 800 mg magnesium daily for 4 weeks has been shown to reduce the perception of fatigue in 25 BCS with HF in an uncontrolled pilot trial [38].

Another important aspect addressed in our study is that a major part of our population was under endocrine therapy for BC. Nobody of them developed worsening side effects and both treatments together were well tolerated. Furthermore, data from an *in vitro* study, show that PureCyTonin does not inhibit CYP2D6 enzyme [14]. On the contrary, other non-hormonal treatments, such as SSRIs and in particular paroxetine, which is the only approved SSRIs for HF's treatment [8], strongly inhibit this enzyme, thus leading to a potential significant reduction of the efficacy of tamoxifen in BCS [39].

A major limitation of our study is the sample size, mainly due to the COVID-19 pandemia. Strengths of this trial are the randomization, the double-blind feature with placebo-controlling, for the first time in a population of BCS.

Conclusion

In conclusion, BCS have to face more severe menopausal symptoms than the healthy menopausal population. Among the alternative options, PureCyTonin seems promising. Our study concerning PureCyTonin is the first double-blind placebo-controlled RCT in BCS. We found that PureCyTonin significantly reduces HF number after 3 months of therapy compared to placebo in BCS and seems to be a well-tolerated treatment, not interfering with adjuvant therapy. Also a subjective improvement in the perception of women regarding the intensity of HF, sweat nuisance, irritability, and fatigue was observed. Further studies are needed on a larger sample size in order to confirm our data.

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Study registration

The study was registered at clinical trials: NCT 05762042

Disclosure statement

Dr. Valentina Elisabetta Bounous had past financial relationships (lecturer) with Pharmaextracta; conflicts of interest are outside the submitted work.

Dr. Silvia Martella had past financial relationships (lecturer) with Theramex Italia and Bayer Italia; conflicts of interest are outside the submitted work.

Prof. Paola Villa had past financial relationships (lecturer, member of advisory boards and/or consultant) with Shionogi Srl, Bromatech and Pharmaextracta; conflicts of interest are outside the submitted work.

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The other authors report no conflicts of interest.

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Data availability statement

The data that support the findings of this study are available from the corresponding author, [VEB], upon reasonable request.

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