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# Purified Cytoplasmic Pollen (PCP) Extract: A Novel Approach to the Treatment of Menopausal Symptoms

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**ABSTRACT**

During the menopause transition, several symptoms such as muscle and joint pain, back pain, vasomotor symptoms, urogenital symptoms, and psychological disorders may occur due to declining estrogen levels. Approximately a third of women would experience severe symptoms with a need for treatment. Currently, menopausal hormonal therapy (MHT) is still considered to be the first-line therapy despite its risk of cancer. Other options, such as pharmacotherapy or herbal formulas, have their limitation, urging the need for an effective and safe treatment. Standardized purified cytoplasmic pollen (PCP) extract, otherwise known as PureCyTonin® is a novel, non-hormonal, non-phytoestrogenic option that is proven to be effective in reducing menopausal symptoms while being neutral to the proliferation and apoptosis of breast cancer cells. Recent evidence shows promising results of PureCyTonin® for menopausal symptoms treatment. **Lyon Clement. Purified Cytoplasmic Pollen (PCP) Extract: A Novel Approach to The Treatment of Menopausal Symptoms.**

**Keywords:** Purified cytoplasmic pollen extract, menopause, PCP.

**ABSTRAK**

Saat transisi ke masa menopause, beberapa gejala seperti nyeri otot dan sendi, nyeri punggung, gejala vasomotor, gejala urogenital, dan masalah psikologis dapat terjadi akibat penurunan kadar estrogen. Sekitar sepertiga wanita akan mengalami gejala berat yang memerlukan terapi. Saat ini, *menopausal hormonal therapy* (MHT) masih dianggap lini pertama, walaupun dengan risiko kanker. Pilihan lain seperti farmakoterapi atau obat-obatan herbal masih terbatas, sehingga masih dibutuhkan terapi yang efektif dan aman. Ekstrak *purified cytoplasmic pollen* (PCP) terstandar, juga dikenal dengan PureCyTonin® merupakan pilihan terapi baru non-hormonal, non-fitoestrogenik, yang telah terbukti efektif meredakan gejala menopause dan bersifat netral terhadap proliferasi dan apoptosis sel kanker payudara. Bukti terkini menunjukkan hasil yang menjanjikan bagi PureCyTonin® untuk terapi gejala menopause. **Lyon Clement. Ekstrak Purified Cytoplasmic Pollen (PCP): Pendekatan Terkini untuk Terapi Gejala Menopause.**

**Kata Kunci:** Ekstrak *purified cytoplasmic pollen*, menopause, PCP.



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**INTRODUCTION**

Menopause is defined as the physiological permanent cessation of menses for 12 months resulting from estrogen deficiency.<sup>1</sup> Menopause begins with the decreasing number of ovarian follicles, followed by inadequate response to the effects of follicle stimulating hormone (FSH). This results in increasing levels of FSH and luteinizing hormone (LH), annihilating LH surge, and in consequence, preventing ovulation. Production of estrogen declines progressively,

followed by the failure of endometrial development, contributing to irregular menstrual cycles until the permanent cessation of the menstrual cycle.<sup>1</sup> Most of the time, women would reach the state of menopause at the median age of 51 years, typically between 45-55 years of age.<sup>1,2</sup>

Several symptoms could appear since the beginning of the transition to menopause. The most reported symptoms are muscle, joint, and back pain, vasomotor symptoms,

such as hot flashes and migraines, urogenital symptoms and sexual disorders, mood changes, and sleep disruption. These symptoms are mainly caused by the decline in estrogen levels.<sup>1,2</sup> Menopause may also increase the risk of certain diseases, including cardiovascular disease, stroke, metabolic syndrome, and osteoporosis.<sup>2,3</sup>

Around a third of menopausal women would experience severe symptoms.<sup>4</sup> According to a multinational study in South East Asia, 1 out

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of 5 women consulted a medical practitioner for menopausal problems, with the 3 most common reasons being the symptoms of headache, insomnia, and dizziness.<sup>5</sup> A study involving 360 Filipino women aged >40 years showed that around 12.5% of women are absent from work because of the symptoms, with joint and muscle pain being the leading cause.<sup>6</sup> Survey on 181 Cambodian women aged 40-60 years showed that negative attitudes toward menopause were mainly observed in perimenopausal women. Menopause is perceived as one of the biggest changes in a woman's life and an unpleasant experience, also believed to be a health issue that requires medical treatment.<sup>7</sup> Menopausal symptoms might negatively impact work productivity and therefore should be treated adequately.<sup>6-7</sup>

### CURRENT MANAGEMENT

Hormonal replacement therapy is considered to be the first-line therapy for menopausal symptoms management. Several options for those who are contraindicated to hormonal replacement therapy include selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), and over-the-counter herbal formulations such as soy extract, red clover, or black cohosh.<sup>8</sup>

### Hormonal Replacement Therapy

Increasing symptoms and risk of certain diseases in menopause are mainly related to estrogen deficiency. Thus, estrogen therapy is a logical solution to address menopause symptoms. Estrogen alone (in selected cases), or more commonly, in combination with a progestogen, is indicated for the relief of vasomotor symptoms and vaginal dryness, and also for the prevention of osteoporosis. Other menopausal symptoms would also benefit from this menopausal hormonal therapy (MHT).<sup>2</sup> In addition, MHT could prevent osteoporosis by maintaining bone mineral density, reducing the risk of fracture in elderly women.<sup>9</sup>

However, MHT is not without its consequences. One of the most feared risks is increased risk of cancer; including breast and endometrial cancer, as both are estrogen-dependent malignancies. Unopposed estrogen (without additional progestogens) is known to increase the risk of endometrial cancer.<sup>9</sup>

Another concern is related to cardiovascular diseases. MHT increases the risk of venous thromboembolism (VTE) and thrombosis-related stroke.<sup>9</sup> While estrogen deficiency may increase the risk of cardiovascular diseases, it is still a controversy whether estrogen replenishment from MHT would reduce the risk of cardiovascular diseases.<sup>9</sup>

### SSRI & SNRI

Both selective serotonin reuptake inhibitor (SSRI) and serotonin-norepinephrine reuptake inhibitor (SNRI) are effective in reducing vasomotor symptoms of menopause, although there is still no direct comparative study. SNRI is associated with more incidence of adverse events compared with SSRI, such as constipation, nausea, and dry mouth. However, in specific patients such as those with a history of breast cancer, SNRI, especially venlafaxine is more recommended than SSRI because SSRI might potentially interact with tamoxifen metabolism, an estrogen antagonist drug commonly used for endocrine therapy in breast cancer patients.<sup>10</sup> Several SSRIs that have been studied to reduce vasomotor symptoms are citalopram, escitalopram, paroxetine, fluoxetine, and sertraline, while SNRIs studied are venlafaxine and desvenlafaxine.<sup>10</sup>

### Phytoestrogens and Black Cohosh

In recent years, phytoestrogen has been used as a complementary therapy. Phytoestrogen demonstrated estrogen-like effects with preferential binding to estrogen receptor  $\beta$ .<sup>9</sup> Phytoestrogen from soy and red clover, for example, is associated with the improvement of menopausal symptoms in several clinical trials, but the results are conflicting.<sup>9</sup> The effect of phytoestrogens on the endometrium and the breast is still unclear, but long-term treatment (up to 5 years) with soy phytoestrogen is associated with an increased incidence of endometrial hyperplasia.<sup>9</sup>

Black cohosh, often presumed to contain phytoestrogen to ameliorate menopausal symptoms, contrarily did not possess any estrogenic activity.<sup>11</sup> This herbal product contained triterpenes with GABA-ergic activity and a serotonin analog, which might be the compound responsible for reducing menopause symptoms.<sup>11</sup> A trial with black cohosh, red clover, or placebo to treat menopausal symptoms was conducted. Although this trial showed black cohosh and

red clover safety for up to 1 year, it failed to show significant improvement in vasomotor symptoms.<sup>12</sup> And black cohosh is also known for its risk of hepatic injury; dozens of case reports of herb-induced liver injury (HILI) were presumably related to the supplementation of black cohosh.<sup>13</sup> The mechanism of liver injury is still uncertain, but one case reported the possibility of autoimmune hepatotoxicity induced by black cohosh.<sup>14</sup>

### Purified Cytoplasmic Pollen (PCP) Extract

Even though MHT is the first-line effective therapy to control symptoms in menopausal women, there are many drawbacks and several patients might prefer non-hormonal and natural approaches.<sup>9</sup> The International Society of Gynecological Endocrinology has supported the use of PureCyTonic<sup>®</sup>, a standardized purified cytoplasmic pollen extract as a non-estrogenic alternative, and its finished products for the treatment of menopausal symptoms with the possibility for use in breast cancer survivors.<sup>15</sup>

Gösta Carlsson, a Swedish gynecologist, first introduced the method of pollen shell removal in the 1940s, retaining the cytoplasm of the grain which contains various nutrients, including proteins, amino acids (including tryptophan, the precursor of serotonin, among others), sugars, minerals, vitamins, and fats.<sup>15</sup> Administration of the cytoplasm extract could revitalize elderly patients.<sup>15</sup> The process of pollen shell removal has been improved and standardized to ensure the reproducibility of every batch, which is now known as purified and specific cytoplasmic pollen extract P182 and GC Fem known as PureCyTonic<sup>®</sup>.<sup>15</sup> This specific pollen extract contains defined pollen monocultures from rye (*Secale cereal*), scots pine (*Pinus sylvestris*), cock's foot (*Dactylis glomerata*), and maize (*Zea mays*).<sup>16</sup>

Regarding the mechanism of action, a study showed that PureCyTonic<sup>®</sup> inhibited the reuptake of [<sup>3</sup>H]-serotonin into rat cortical synaptosomes in a dose-dependent manner, similar to the mechanism of action of SSRIs.<sup>17</sup> However, the main difference from SSRIs is that this natural product did not demonstrate interference with CYP2D6, therefore eliminating the possibility of drug interaction with tamoxifen.<sup>17</sup> In addition, PureCyTonic<sup>®</sup> has no estrogenic activity in a study based on immature rat uterotrophic bioassay.<sup>18</sup>



### Evidence-based Data of PCP Extract for Menopausal Symptoms

A prospective study was performed on 104 menopausal women. They received PCP extract containing PI82 and GC Fem (Serelys<sup>®</sup>) in a dose of 160 mg with 5 mg vitamin E twice daily for 3 months. The study showed that the use of Serelys<sup>®</sup> is associated with a significant decrease in multiple menopausal symptoms, including hot flashes, sleep disturbance, depressive mood, irritability, fatigue, vaginal dryness, and muscle and joint pain ( $p < 0.0001$ ) within 3 months of therapy. No undesirable side effects are reported in this study.<sup>16</sup>

These results are consistent with the clinical findings of previous RCT including 54 subjects comparing similar products of PCP extract containing PI82 and GC Fem (Femal<sup>®</sup>) 320 mg once daily in the morning with placebo. The results showed that 65% of subjects taking Femal<sup>®</sup> responded with a reduction in hot flashes compared with 38% in the placebo group ( $p < 0.006$ ). Subjects also showed better quality of life ( $p < 0.031$ ).<sup>19</sup>

Another prospective observational study compared herbal remedies from pollen extract with soy isoflavones or no treatment for 164 women suffering from menopausal symptoms (based on the Kupperman index) and sleep disturbances (based on the Pittsburgh sleep quality index/PSQI). Both treatments resulted in significant improvement in the

Kupperman index ( $p < 0.001$ ) after 3 months and 6 months of treatment. A greater decrease in daily hot flashes and better improvement of the Kupperman index are observed in subjects receiving pollen extract compared with soy isoflavones (both  $p < 0.001$ ). Likewise, improvement of sleep quality was more evident in the pollen extract group compared to the soy isoflavones group after three (-24.7% vs. -9.3%;  $p < 0.001$ ) and six months (-52.9% vs. -4.0%;  $p < 0.001$ ).<sup>20</sup>

### PCP Extract for Menopausal Symptoms in Women with Breast Cancer

As previously stated, PCP extract has no estrogenic activity in a study based on immature rat uterotrophic bioassay.<sup>18</sup> Seeger, et al, then studied Serelys<sup>®</sup> further in human breast cancer cells, whether it affects their proliferation and apoptosis, compared with estradiol and growth factor for six days of stimulation. The human breast cancer cell lines used in this study are MCF-7, an ER+ and PR+ invasive breast ductal carcinoma cell line, and T47D, a human ER+ primary breast cancer cell line. Both are also transfected with progesterone receptor membrane component-1 (PGRMC1), the other receptor that could be affected by estrogen. The study showed that in contrast to estradiol and growth factor, Serelys<sup>®</sup> did not significantly affect all breast cancer cell lines proliferation and apoptosis, proving its neutrality. Unsurprisingly, the growth factor increased

cells' proliferation the most, while anti-apoptotic activity was increased by estradiol the most.<sup>21</sup>

Recently, PCP extract was also studied in a case series of 12 women with breast cancer. After 3 months of treatment with Femal<sup>®</sup> containing 320 mg PCP extract daily, all women had an improvement in hot flashes, cardiac symptoms, irritability, and anxiety symptoms without any additional side effects. Tolerance was excellent during the study, which was evaluated by the European Organization for Research and Treatment of Cancer (EORTC) score.<sup>22</sup> Further research is needed, but the use of PCP extract to treat menopausal symptoms in women with a history of breast cancer seemed to be promising.<sup>15,18,21-22</sup>

### CONCLUSION

Standardized PCP extract containing PI82 and GC Fem, otherwise known as PureCyTonin<sup>®</sup> and its finished products, Femal<sup>®</sup> and Serelys<sup>®</sup> are novel and effective treatments in ameliorating the symptoms of menopause with favorable safety profile. PureCyTonin<sup>®</sup> and its finished products are non-hormonal, non-phytoestrogenic, and proven to be neutral regarding breast cancer cell proliferation and apoptosis, thus could be an option for menopausal symptoms control in breast cancer patients.

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