

The safety and tolerance of phytotherapies in menopausal medicine – a review of the literature

Piotr Czuczwar, Tomasz Paszkowski, Marek Lisiecki, Sławomir Woźniak, Anna Stępnia

3rd Chair and Department of Gynecology, Medical University of Lublin, Poland

Abstract

Phytoestrogens are polyphenol, non-steroidal substances of plant origin, resembling 17 β -estradiol in structure. These substances can act as either agonists or antagonists of oestrogen receptors α and β . Phytoestrogens are widely used to alleviate menopausal symptoms, such as hot flushes and night sweats. Most of the currently available products of plant origin registered to soften climacteric symptoms consist of extracts obtained from soy, red clover, or black cohosh.

Non-hormonal phytotherapy is a new alternative for patients suffering from menopausal symptoms. Active ingredients such as PI 82-GC FEM extract do not show any direct hormonal mechanisms of action typical for oestrogens and phytoestrogens.

There are concerns about the safety and tolerability of phytoestrogens. In this review we summarise the current literature regarding the clinical aspect of safety and tolerance of different phytotherapies used to relieve menopausal symptoms.

Key words: phytoestrogens, menopause, phytotherapy.

Introduction

Phytoestrogens

Phytoestrogens are polyphenol, non-steroidal substances of plant origin, resembling 17 β -estradiol in structure. These substances can act as either agonists or antagonists of oestrogen receptors α and β (ER α and ER β) [1, 2].

The affinity of phytoestrogens is considered to be sevenfold greater to ER β than to ER α [3, 4]. The biological activity of isoflavones on ERs depends on the level of endogenous oestrogens: at high levels of endogenous oestrogens the isoflavones exert antagonistic properties, while at low levels they act as ER agonists [3].

Phytoestrogens are divided into three major classes:

- Lignans (secoisolariciresinol and matairesinol)
- Stilbene (resveratrol: found in the skin of many fruits, inter alia grapes and wines)
- Flavonoids (isoflavones, which include four subgroups: isoflavones, isoflavanones, isoflavanes, and coumestans)

Most of the available studies focus on three phyto-hormones: isoflavones, lignans, and coumestans. These compounds can be found in different plants, their biological activity also varies:

- Isoflavones – present mainly in soy, lentils, chickpeas, beans, broad beans, hops, and cereals, including wheat, barley, and rye.

- Lignans – found in seed oils (mainly linseed oil), but they are also present in sunflower seeds, linseeds, garlic, onion, cherries, pears, apples, hop beer, and red wine.
- Coumestans derivatives (coumestans) – not present in the ingredients of standard diets. These compounds can be found mainly in red clover and, in lower concentrations, in sunflower seeds and soy sprouts.

The richest sources of isoflavones (genistein, daidzein, formononetin, biochanin A, glycitein) are mainly leguminous vegetables (soy and its preserves, leguminous vegetables seeds, lentils, spinach, and red clover).

Non-hormonal phytotherapy

Non-hormonal phytotherapy is a new therapeutic alternative for patients suffering from menopausal symptoms. The most promising preparation is a dietary supplement composed of standardised extracts from pollen and pistil (PI 82-GC FEM) combined with Vitamin E as an antioxidant.

The PI 82 extract is obtained from pollen of *Secale cereale*, *Dactylis glomerata*, and *Pinus silvestris*. PI 82 also consists of extracts from *Zea mays* pollen and pistil. The other active compound included in Femelis Meno[®]'s GC FEM, which is an extract from *Secale cereale*, *Zea mays*, and *Pinus silvestris* pollen. Pollen and

pistil are selected and collected separately using a standardised method. Cultivation of selected plant species is led under strict supervision, similarly to the process of extraction of active substances. This product was introduced to the Swedish market in 1995 and is now available in 15 countries, including Poland. The efficacy of this preparation in decreasing vasomotor menopausal symptoms was discovered accidentally during a clinical study evaluating its generally strengthening effect in elderly patients [5].

The PI 82-GC FEM extracts do not show any direct hormonal mechanisms of action typical for oestrogens and phytoestrogens. It is suggested that PI 82-GC FEM extracts act similarly to SSRIs by modulating the activity of serotonergic neurons in the central nervous system, which control thermoregulation, mood, and sleep. It was found that PI 82-GC FEM extracts obtained from pollen and pistil inhibit serotonin uptake in rats' cortical synaptosomes [5].

Tolerability and safety of phytoestrogens

The safety and tolerance of long-term supplementation with phytoestrogens of soy origin and isoflavones from black cohosh and red clover remain controversial.

Red clover

A study comparing the occurrence of adverse reactions in women using red clover extract and placebo did not show any significant differences (RR 0.95, 95% CI: 0.65 to 1.40) [6]. Moreover, no statistical differences were found in the occurrence of respiratory tract infections, headaches, muscle aches, sicknesses, joint pains, diarrhoeas, and abnormal uterine bleeding.

Three studies investigated the possible impact of red clover on endometrial thickness [7-9]. Baber *et al.* did not observe significant differences in endometrial thickness after 12 weeks of red clover treatment. Interestingly, Imhof *et al.* demonstrated a significant decrease in endometrial thickness (by approximately 15%) after three months of red clover treatment in comparison to placebo ($p < 0.001$) [7]. No differences in endometrial thickness were observed in this study among patients using red clover or placebo [8].

Soy

Among the six studies evaluating the frequency of adverse reactions in women consuming meals rich in soy, five did not reveal any significant alterations in comparison to the subjects on soy-poor diet. However, in one study 75% of women using the soy-rich diet reported bloating, sickness, body weight gain, and gastrointestinal disturbances, in contrast to the placebo

group, in which these symptoms occurred in only 17% of women [10].

Most of the studies investigating the safety of soy extracts did not show any influence of soy extracts on endometrial thickness, vaginal maturation index, and occurrence of adverse reactions in comparison to placebo. Kaari *et al.* observed a significant improvement in vaginal pH and vaginal maturity index in patients using oestrogen therapy in comparison to those using soy extract [11]. On the other hand, soy extracts produced less endometrial stimulation and fewer adverse reactions (such as uterine bleeding). Another study showed that soy extract has a positive effect on vaginal pH in comparison to placebo [12].

One study demonstrated a significant increase in the percentage of constipation and fractures in patients using soy extracts in comparison to placebo [13]. However, the authors concluded that the increased incidence of fractures was not directly related to the treatment option. Fritz *et al.* suggested that soy consumption may result in a decrease of breast cancer morbidity, recurrence, and mortality [14].

Three of the available studies reported a significant increase in the occurrence of adverse reactions in patients treated with soy extracts [10, 13, 15]. Soy extract powder resulted in taste aversion, which probably resulted from the product type [10]. Levis *et al.* evaluated the influence of soy on bone mass loss and vasomotor symptoms [13]. Surprisingly, the incidence of fractures was significantly higher in the group of women taking soy diet supplements.

The results of a few publications suggest that a carcinogenic action of long-term soya isoflavones cannot be excluded. Shike *et al.* showed that exposure to soy genistein enhances the gene expression in the MCF7 cells of breast cancer, which may initiate the carcinogenesis [16]. De Lemos published a meta-analysis of studies published between 1966 and 2001, which revealed that soy origin genistein and daidzein even in low concentrations can stimulate the growth of malignant breast tumours in both an *in vitro* model and in animal experiments. Moreover, these isoflavones were shown to weaken the antineoplastic action of tamoxifen. In conclusion of this meta-analysis, caution is recommended in using soya isoflavones in patients during or after breast cancer treatment [17].

Black cohosh

Black cohosh vs. placebo

Several studies investigating adverse reactions to black cohosh have been published [18-23]. In a group of 430 women treated with black cohosh a total of 194 adverse reactions were observed (0.45 per patient), while in the placebo group (392 patients) – 195 (0.50

per patient). No significant differences in the incidence of adverse reactions were found in the group of women using black cohosh.

Black cohosh vs. hormonal therapy

Four studies analysed the safety profile of black cohosh in comparison to hormonal therapy [19, 23-25]. In the group of 253 women taking black cohosh a total of 202 adverse reactions were noted (0.80 per person) in comparison to 304 reactions among 208 women using hormonal therapy (1.46 per person). However, this difference was not statistically significant.

In terms of safety, black cohosh was also compared to red clover and fluoxetine – these isolated reports do not allow firm conclusions to be drawn.

A review of literature concerning black cohosh safety included a total of 4232 women. Adverse reactions due to the use of black cohosh (6.5 to 160 mg) with a follow-up ranging from one to twelve months were reported. The observed adverse reactions were relatively rare, mild, and transient. The most commonly reported adverse effects were related to the gastrointestinal system, musculoskeletal system, and connective tissue [26]. Individual cases of hepatitis, hepatic insufficiency, facial oedema, and cutaneous vasculitis were also noted, but there is no evidence of a causal relationship between these adverse reactions and black cohosh [27].

Tolerance and safety of non-hormonal phytotherapy

One of the main concerns in the context of PI 82-GC FEM extract safety profile is the possibility of allergic reactions due to the strong allergic properties of pollen. However, during the extraction process purified cytoplasm of pollen cells is obtained by removing the coat, which consists mainly of allergens. The allergens that are present in pollen are completely removed, which is why this product may also be used in patients with various allergies. After such processing pollen cytoplasm consists almost completely of bioactive substances that have a very high bioavailability following oral intake.

The safety profile of PI 82-GC FEM extracts has been evaluated by several studies. Elia and Mares examined 417 women suffering from menopausal symptoms (average age: 54.4 years), mainly of vasomotor origin. These patients were treated with a drug containing 40 mg of GC FEM extract, 120 mg of PI 82 extract, and 5 mg of Vitamin E (two pills per day) for 84 days. More than 98% of the study participants reported the tolerance of this therapy to have been very good [28].

Winther *et al.* conducted a randomised, placebo-controlled study in which the efficacy of PI 82-GC FEM extracts in decreasing menopausal symptoms (mainly hot flushes) was evaluated. Fifty-four women randomised to

three-month treatment with PI 82-GC FEM extracts or placebo were included in the study. Only minor and clinically insignificant adverse events were noted, and the tolerance profile of this product was evaluated to be very good [29].

Kimura and Gruber investigated a product containing PI 82-GC FEM extracts and confirmed its efficacy in reducing menopausal symptoms, such as hot flushes (average reduction of 57.3%), night sweats (average reduction of 62.6%), and sleep disorders (average reduction of 54.7%). No adverse events were found in this study, including allergic reactions [30].

Purified Swedish pollen extract seems a very interesting treatment option in breast cancer patients treated with tamoxifen. Tamoxifen treatment may result in the onset or exacerbation of vasomotor symptoms. However, such patients should not receive systemic oestrogens or phytoestrogens because these compounds may have a proliferative effect on breast cancer cells. Currently, selective serotonin reuptake inhibitors (SSRIs) are approved for treatment of tamoxifen-induced vasomotor symptoms. Unfortunately, SSRIs may interfere with the efficacy of tamoxifen by inhibiting CYP2D6, a member of the cytochrome P450 enzyme family, which is crucial in the metabolism of tamoxifen [31]. Interestingly, in an *in vitro* study Swedish pollen extract did not inhibit CYP2D6 [32]. Taking into consideration that Swedish pollen does not act by hormonal mechanisms and does not inhibit the activity of CYP2D6, it seems a reasonable option for the prevention and treatment of vasomotor symptoms in breast cancer patients receiving tamoxifen.

The Polish Menopause and Andropause Society (PMAS) recently published a statement concerning a product containing PI 82-GC FEM extracts. According to the PMAS Expert Team statement, available literature provides evidence that the efficacy and safety profile of PI 82-GC FEM extracts used in order to reduce menopausal symptoms is favourable [5].

Conclusions

Current literature concerning the safety and tolerance profile of phytoestrogens provides equivocal results – further studies are required to provide firm evidence, especially regarding the use of soya isoflavones in breast cancer survivors. A non-hormonal phytotherapeutic option should be taken into consideration when treating patients with vasomotor menopausal symptoms, especially in cases where the safety of the therapy is of special importance.

Disclosure

Authors report no conflict of interests.

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