

## The clinical use of a preparation based on phyto-oestrogens in the treatment of menopausal disorders

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**Abstracts.** In order to evaluate the efficacy of soya isoflavones (genistein and daidzein) in the treatment of the principal menopausal disorders, a double blind randomized study was performed on a sample of 50 women (with an average age of  $53,3\pm 3,1$  years) with Climateric syndromereferred to the I Clinica Ostetrica e Ginecologica, Policlinico Umberto I, Roma. The research protocol involved the random subdivision of the enrolled sample into two groups of 25 women, group 1 (with an average age of  $53,3\pm 3,5$  years, and an average menopausal age of  $51,6\pm 1,8$  years) and group 2 (with an average age of  $53,1\pm 2,9$  years, and an average menopausal age of  $51,3\pm 1,2$  years), who were to receive treatment for three months with the product being studied and with a placebo. After the three-month period, as an additional check, the group initially treated with the placebo would move to the phyto-oestrogens and viceversa. All of the patients were subjected to a series of clinical and instrumental examinations and were asked to fill in a questionnaire concerning their complaints, at the start, at halfway (third month) and at the end (sixth month) of the trial. The results of the evaluation of the questionnaires performed on the 47 patients who had completed the trial showed, in the first three months, an improvement in the symptoms (hot flushes) in 11 patients treated with phyto-oestrogens against 6 patients from the group that received only the placebo. In the second three-month period the hot flushes reappeared in 4 of the 11 patients who had previously seen improvements and had then passed to the placebo. In contrast, the group that passed to the phyto-oestrogens, after treatment with the placebo, experienced the disappearance of hot flushes in 11 women, including the 6 who had already improved in the first three months. There was no significant reduction in anxiety, insomnia or vaginal dryness. None of the enrolled patients indicated complaints linked to the treatment. It can be concluded that the use of a product based on phyto-oestrogens, such as the one experimented, can lead to a significant reduction in some of the disorders linked with the menopause, especially hot flushes.

**Key words:** Menopause, vasomotor disorders, phyto-oestrogens, genistein

### Introduction

The climacteric or menopause is one of the most critical periods in the life of a woman, and leads to a series of disorders which are usually transitory, but in some cases are serious enough to require pharmacological treatment. From this point of view there are two clinical events of particular importance: the so-called Climacteric syndrome, characterized by vasomotor crises, paraesthesia, insomnia, depression, vertigo, pal-

pitations, which usually disappear in a year, and the Oestrogenic deficiency syndrome which, on the other hand, has burdensome and progressive characteristics, with atrophy of the secondary sexual characteristics, dyspareunia, urinary incontinence, pollakiuria and osteoporosis. In general the Oestrogenic deficiency syndrome requires pharmacological treatment based on oestrogens in accordance with protocols which involve association with progestins. The oestrogens limit the appearance of sympathetic system phenome-

na and osteoporosis, and the association with progestins increases the efficacy of the treatment and reduces the risk of typical and atypical hyperplasia in non-hysterectomized patients (1). In any case, it should be remembered that oestrogens have an effect on only some of the disorders linked with the menopause, and in particular on vasomotor disorders, on vaginal dryness and on osteoporosis. At the same time, however, there is an increased risk of endometrial carcinoma and, to a lesser extent, carcinoma of the mammary (2-5). Above all, they do not appear to be very effective in tackling disorders such as anxiety, depression, irritability and asthenia. In these cases, on the other hand, it is advisable to seek psychological support and, if necessary, the prescription of psychoactive drugs.

According to the recent WHI report (6), it would seem that oestrogens do not have a protective action against cardiovascular risk, an action which, on the other hand, has been demonstrated in soya derivatives.

Currently, therapy with oestrogens remains an effective instrument available to the clinician in tackling the typical disorders found in both the Climacteric syndrome and the Oestrogenic deficiency syndrome (7).

More recently, proposals have been made concerning a class of oestrogenic analogues, of vegetal derivation, of potentially high therapeutic interest: these are the so-called phyto-oestrogens (8). Phyto-oestrogens are substances of vegetal origin with oestrogenomimetic activity, that are able to bind with the oestrogenic receptors, though to a lesser extent than the true oestrogens. This information, together with the fact that their oestrogenic activity is milder than that of human oestrogens, makes it impossible for phyto-oestrogens to perform systemic effects while the endogenous oestrogens are predominant in the circulation. On the other hand, when, with the arrival of the menopause, the production of these hormones falls naturally, the phyto-oestrogens taken in with the diet or as a supplement can exercise their effects, reducing the characteristics that are symptomatic of the deficiency (9). These substances are present in nature in the form of isoflavones found above all in some legumes such as soya (10) and red clover (11), which are

typical dietary elements especially in east Asia, where it is estimated that the daily intake of these substances is about thirty times greater than the experience in Western populations (12). Among the principal isoflavones found in the soya seed extract (glycine wax), we have daidzein and above all genistein, which has an analogo-oestrogenic activity about 10 times milder than oestradiol. Numerous epidemiological and experimental studies confirm the beneficial effects of phyto-oestrogens on the human organism. From the first view point, data published by Notelovitz in 1989 (13) highlight how in Japan (where there is a high consumption of soya in the diet), the percentage of women in menopause who suffer from oestrogen deficiency disorders is enormously reduced in comparison with that which occurs in the West (25% vs 85%). On the experimental front we cite one double blind vs placebo trial conducted by Albertazzi et al. in 1998 (14), on 104 women in the initial phase of menopause. In this trial it was seen that the daily consumption of 60 g of soya extract made it possible to reduce the incidences of vasomotor disorders to a statistically more significant degree when compared with the consumption of the placebo, without any particular side effects. In addition, evidence is progressively being accumulated confirming the beneficial effect of the soya isoflavones on the lipidic pattern (15, 16), beneficial effects on the prevention of certain types of tumour (cancer of the prostate and mammary) and postmenopausal osteoporosis (17) have not yet been confirmed. It would appear that phyto-oestrogens act as anti-tumour agents because of both their antioxidant action and their inhibitory action on certain enzymes expressed by the oncogenes. In addition, it seems that phyto-oestrogens act as antiproliferatives by binding competitively with the oestrogen receptors, thus stimulating the hepatic production of "sex hormone binding globulin" and, as a consequence, reducing the quantity of free, i.e. active, oestrogens. The widespread interest that this class of substance has provoked among doctors is therefore understandable. Above all, their effect, which is milder than that of the synthetically prepared homologues, appears to be particularly suitable for the treatment of not particularly serious borderline forms of Climacteric syndrome, where there could be legitima-

te doubts as to whether it is worth starting a true replacement therapy with all of the related risks. In addition, the concern of the public when faced with all those remedies perceived as “natural” cannot be undervalued a priori, but should be correctly orientated by the doctor towards that real group of therapies that some Authors are starting to refer to as “rational phytotherapy” (18).

On these grounds, it seemed to be of particular interest to evaluate the true efficacy of a treatment based on phyto-oestrogens in a sample of women who had recently started to suffer from Climacteric syndrome.

## Materials and methods

In order to evaluate the therapeutic efficacy of the consumption of products based on phyto-oestrogens, and any side effects, in a group of women suffering from Climacteric syndrome, a double blind randomized trial was performed comparing a commercially available preparation based on phyto-oestrogens (Fitormil) against a placebo. The product under examination is a compound that we describe in Table 1. It is important to point out the presence of about 32

**Table 1.** Fitormil composition and technical features

**Ingredients:** Soya oil - *Thickeners:* partially hydrogenated soya oils and cera flava - 40% soya isoflavones (80 mg/capsule) - Extract of *cimicifuga racemosa* (30 mg/capsule)

*Emulsifier:* lecithine - Vitamin D.

**Coating:** gelatine - resistance agents: glycerol and sorbitol - *Colourants:* E 141 and E 171 (titanium bioxide).

### NUTRITIONAL ANALYSIS

Energy value	Per 100 g	Per cps	RDA%
Kcal	580.8	4.6	
Kj	2432.0	19.2	
Average composition			
Proteins (N x 6.25)	16.3 g	0.13 g	
Carbohydrates	7.7 g	0.06 g	
Fats	55.9 g	0.44 g	
Isoflavones	4.0 g	32.00 mg	
Vitamin D	0.6 mg	5.00 mcg	100

**Clinical trials:** research conducted at Policlinico Umberto I - I Istituto di Clinica Ostetrica e Ginecologica - Università “La Sapienza”, Roma

mg of soya isoflavones in each capsule, in addition to 5 mcg of Vitamin D, providing 100% of the daily recommended dose (Fitormil, product insert).

The primary End-point of the trial was to quantify after a period of six months the effects of the therapy based on phyto-oestrogens on the principal disorders typical of Climacteric syndrome. A second study will extend the trial up to 12 months to evaluate the effects of the therapy on the lipidic pattern and on the state of bone mineralization. The trial protocol involved the enrolment of 50 women referred to the I Clinica Ostetrica e Ginecologica del Policlinico Umberto I di Roma.

The criteria for inclusion were the following:

- Between 48 and 54 years of age
- Recent menopause (for at least one year and for no more than three years)
- Caucasian race
- Negative PAP test
- Pelvic ultrasound within the norm (endometrial echopattern  $\leq 4$  mm)
- The presence of disorders that justify the diagnosis of Climacteric syndrome.

The criteria for exclusion were the following:

- Previous surgery for genital or mammary neoplasia
- Already undergoing hormonal therapy or off such therapy for less than six months
- Arterial hypertension and/or cardiovascular pathologies
- Endocrinological pathologies
- Nicotinism
- Obesity
- Abuse of alcohol or narcotics.

At the moment of enrolment all of the patients were subjected to a case history study, a general objective examination, blood chemistry tests as set out in the protocol, PAP test, vaginal cytology (pyknotic index), pelvic ultrasound, breast ultrasound, mammography and MOC. At the beginning of the trial, the patients were also asked to fill in a questionnaire on the symptoms associated with the menopause.

The 50 enrolled women (with an average age of 53,3 $\pm$ 3,1 years and an average age at the onset of menopause of 51,4 $\pm$ 1,6 years) were then randomly divi-

**Table 2.** Characteristics of the whole sample and of each treatment group

	Whole group	Group 1	Group 2	
Number of subjects	50	25	25	
Average age (years)	53,3±3,1	53,6±3,5	53,1±2,9	n.s.
Average menopausal age (years)	51,4±1,6	51,6±1,8	51,3±1,2	n.s.
BMI	26,3±2,6	26,8±1,9	25,9±1,1	n.s.

n.s.: the differences between each group are not statistically relevant

ded into two homogeneous groups of 25 women each (Group I and Group II) (Table 2). Following the protocol, the first group was treated for three months with preparation A (Fitormil) and for the next three months with preparation B (placebo). The second group, on the other hand, followed an inverse programme: first three months preparation B and second three months preparation A.

After the first three months of the trial, all of the women were subjected to a clinical examination including anamnesis, general objective examination and the compilation of a questionnaire on the symptoms associated with the menopause.

Finally, at the end of the trial all of the patients were again subjected to a clinical examination including anamnesis, general objective examination, blood chemistry tests, PAP test, vaginal cytology, pelvic ultrasound, breast ultrasound, MOC. They were also asked to fill in the above-mentioned questionnaire on the symptoms associated with the menopause.

The efficacy of the treatment on the individual patients was evaluated by processing the questionnaires filled in by the patients in binary terms (improvement/no improvement of the symptoms during the trial).

An analysis of the effects of the treatment was then made comparing (via the Student T Test) the efficacy of the product containing phyto-oestrogens against the placebo in each of the two groups, and comparing the effects obtained on the two different groups of patients receiving the same treatment (1st three-month period group I vs 2nd three-month period Group II and 2nd three-month period group I vs 1<sup>st</sup> three-month period group II, respectively).

It has already been decided to continue the trial

for another six months in order to evaluate any changes in the bone mineralization and lipaemic profiles, which in some patients had already shown alterations in the recruitment phase, but without significant changes after three and six months.

## Results

Of the 50 enrolled women, one left the trial because of the onset of non-hormone-dependent neoplastic pathology; one patient left the trial because of an intense vegetative syndrome which failed to decrease; finally, one patient left the trial for spotting after 15 days. Therefore 47 patients completed the trial.

As expected, no cases were recorded of changes in the blood chemistry parameters, the PAP test, cytological tests, the MOC and the pelvic and breast ultrasound examinations during the trial.

On the other hand, when the questionnaires concerning the symptoms experienced by the patients were examined, interesting data emerged, in particular as regards the vasomotor disorders (hot flushes). In Group I, which started the trial with 25 patients initially treated with the product based on phyto-oestrogens for three months, there was only one drop-out case for spotting on the 15<sup>th</sup> day, whereas with the 24 remaining patients, 11 described an improvement in the symptoms related to vasomotor disorders, on average within the second month of therapy (Table 3). In Group II, which also started the trial with 25 patients, initially treated with the placebo, there were two drop-out cases, a few days after the start of the trial, for poor compliance with the protocol. Of the remaining 23 patients, 6 described an improvement in their general symptoms (Table 4).

In the second three months of the trial, during which the patients in Group I passed from the product containing phyto-oestrogens to the placebo, the disorders appeared in 4 of the 11 patients who had previously improved (Table 5). In Group II, which passed from the placebo to the product containing phyto-oestrogens, the hot flushes disappeared in 11 of the 23 patients treated, including the 6 who had already experienced an improvement in the first three months (Table 6).

**Table 3.** Preparation A. Months: June-July-August

Patient	Result
1	improvement after 2 months
2	improvement after 6 weeks
3	<i>drop-out</i>
4	no improvement
5	no improvement
6	improvement
7	no improvement
8	improvement after 6 weeks
9	improvement after 2 months
10	no improvement
11	no significant improvement
12	improvement after 4 weeks
13	no improvement
14	improvement after 2 months
15	improvement after 2 months
16	no improvement
17	no improvement
18	improvement after 70 days
19	improvement after 80 days
20	no improvement
21	no improvement
22	improvement after 60 days
23	no improvement
24	no improvement
25	no improvement

**Table 4.** Preparation A. Months: September- October-November

Patient	Result
1	improvement after 2 months
2	hot flushes
3	hot flushes
4	no hot flushes
5	hot flushes
6	no hot flushes
7	<i>drop-out</i>
8	improvement after 2 months
9	improvement
10	no hot flushes
11	hot flushes
12	hot flushes
13	no hot flushes
14	improvement after 80 days
15	hot flushes
16	hot flushes
17	hot flushes
18	no hot flushes
19	<i>drop-out</i>
20	improvement
21	hot flushes
22	no hot flushes
23	hot flushes
24	hot flushes
25	hot flushes

**Table 5.** Preparation B. Months: September- October-November

Patient	Result
1	re-emergence of hot flushes
2	no hot flushes
3	<i>drop-out</i>
4	hot flushes
5	hot flushes
6	no hot flushes
7	hot flushes
8	no hot flushes
9	re-emergence of hot flushes
10	hot flushes
11	hot flushes
12	no hot flushes
13	hot flushes
14	re-emergence of hot flushes
15	no hot flushes
16	hot flushes
17	hot flushes
18	re-emergence of hot flushes
19	no hot flushes
20	hot flushes
21	hot flushes
22	no hot flushes
23	hot flushes
24	hot flushes
25	hot flushes

**Table 6.** Preparation B. Months: June-July-August

Patient	Result
1	no improvement
2	no improvement
3	no improvement
4	improvement
5	no improvement
6	improvement
7	<i>drop-out</i>
8	no improvement
9	no improvement
10	improvement after 2 months
11	no improvement
12	no improvement
13	improvement after 2 months
14	no improvement
15	no improvement
16	no improvement
17	no improvement
18	improvement
19	<i>drop-out</i>
20	no improvement
21	no improvement
22	improvement after 60 days
23	no improvement
24	no improvement
25	no improvement

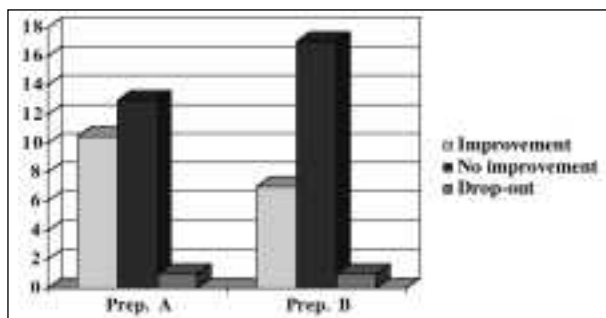


Figure 1. Group I patients treatment

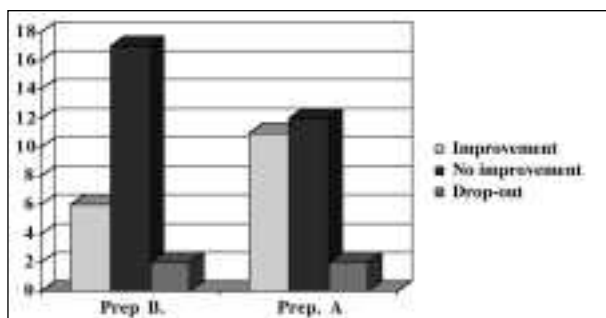


Figure 2. Group II patients treatment

Figure 1 shows the number of patients in Group I who described, or did not describe, improvements in the symptoms during the first and second three-month periods. The Student Test T highlights a statistically significant difference between the number of patients who described improvements in the first three-month period (treatment with phyto-oestrogens) compared with those who described improvements in the second three-month period (placebo) (11 vs 7;  $p < 0.05$ ).

In the same way Figure 2 shows the number of patients in Group II who described, or did not describe, improvements in the symptoms during the first and second three-month periods. The Student Test T highlights a statistically significant difference between the number of patients who described improvements in the second three-month period (treatment with phyto-oestrogens) compared with those who described improvements in the first three-month period (placebo) (11 vs 6;  $p < 0.05$ ).

On the other hand, there were no significant re-

ductions in other disorders such as anxiety, insomnia and vaginal dryness.

Finally, it should be indicated that during the trial none of the patients described undesired effects and the consumption of the capsules was generally well tolerated, no gastroenteric disorders being described.

On the basis of these observations we can therefore conclude that treatment based on phyto-oestrogens, such as the one tested by us, is able to lead to an improvement in some of the typical symptoms of the Climacteric syndrome, with particular reference to vasomotor disorders, to a statistically significant degree when compared with placebo treatment and, over the period of the trial, the treatment did not produce any side effects.

## Conclusions

The period of the menopause is a particularly critical phase in the life of a woman, often characterized by disorders which cannot be ignored and are serious enough for the doctor to use pharmacological hormone replacement therapies or support therapies.

Such a procedure, now widely agreed upon in cases in which the clinical picture appears to be of such severity as to be described as a true case of Climacteric syndrome or, worse still, Oestrogenic deficiency syndrome, can however prove to be not well accepted in those borderline cases where the extent of the disorders is less clear. In fact, it is in these cases that the possibility of side effects, that cannot be ignored, can lead to doubts in the patient and the doctor, concerning the true cost/benefit balance of the traditional treatment based on oestrogenic hormones.

On the other hand the recent availability of natural products which, when taken orally, can be transformed in the intestine into bioavailable phyto-oestrogens, seems to offer the clinician an additional therapeutic instrument, certainly less pharmacologically potent than the synthetic analogues but, at the same time, easier to handle and use especially in those cases where an approach perceived as "natural", even though conducted within the modern field of rational phytotherapy, could be more acceptable to the pa-

tient. In fact, the impact that disorders linked to the menopause, even borderline, can have in subjects who are already living through a psychologically delicate period should not be underestimated.

In this context, the data that we present, which could certainly be amplified, seem to confirm the efficacy of phyto-oestrogens in tackling climacteric disorders of vasomotor origin, without significant side effects. It is clear that the therapeutic approach that could result from such observations is certainly not decisive: for example, the problem of disorders of psychological origin (anxiety, insomnia, etc.) remains, and here sometimes not even synthetic oestrogens are effective.

At the same time it is fundamental that the companies trading in products based on phyto-oestrogens share the titration procedures of their products as soon as possible, so as to offer the clinician making the prescription as much information as possible in terms of the exact chemical composition of the product and the true dosage given. This being said, we can conclude that the clinical use of products based on phyto-oestrogens, such as that experimented by us, certainly appears to be effective and risk-free in women suffering from mild Climacteric syndrome disorders.

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