



Randomized clinical trial comparing conjugated equine estrogens and isoflavones in postmenopausal women: a pilot study

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Abstract

Objective: The aim of this study was to evaluate the effects of isoflavone on the climacteric symptoms (Kupperman Menopausal index), vaginal pH, vaginal cytology (vaginal maturation index) and endometrium (evaluated by ultrasound and biopsy) in postmenopausal women.

Methods: It was a single-center, 6-month, randomized, double-blind, estrogen-controlled trial. Seventy-nine women were randomly assigned to one of the two treatment groups: isoflavone ($n = 40$): 300 mg of the standardized soy extract with a medium dose of 120 mg isoflavones/day as glycoside and aglycone (60 mg twice a day), or estrogen ($n = 39$): one capsule of 0.625 mg conjugated equine estrogens and other capsule with glucose 0.625 mg (placebo).

Results: After treatment, there was a decrease in the symptomatology in both estrogen and isoflavone groups. There was a significant decrease in vaginal pH, an increase in superficial vaginal cells and endometrium proliferation after 3 and 6 months of treatment in the estrogen group, but no differences were observed in the isoflavone group for these variables.

Conclusions: We concluded that the daily standardized soy extract with 120 mg isoflavones' effect on symptoms was similar to that from estrogen. Soy isoflavone has no effect on endometrium and vaginal mucosa during the treatment.

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Keywords: Isoflavone; Postmenopausal women; Hormone therapy

1. Introduction

Hormone therapy (HT) and estrogen therapy (ET) have been the most common therapies for menopausal and genitourinary symptoms [1–3]. However, these regimens have been reported to increase the risk of breast (HT) and endometrial cancers (ET), and also

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present a number of side effects such as breast tenderness, thromboembolic events and uterine bleeding [4–6]. These facts may be the reason for the low compliance of these hormonal treatments. Given the relatively low prevalence of current HT use, alternative strategies are being evaluated [7].

Epidemiological data indicate that fewer than 25% of Japanese and 18% of Chinese climacteric women [8,9] complain of hot flushes, compared to 85% of North American women [10] and 75% of European women [11]. Furthermore, Asian women have a lower incidence of estrogen-related cancers, cardiovascular disease and osteoporosis when compared to western women [12,13]. Many theories have been proposed to explain these differences, such as a diet rich in isoflavones.

Isoflavones belong to a class of phytoestrogens that are found in soybeans, lentils, chickpeas and red clover [14]. Soybeans are a rich source of isoflavones and include the biochemicals genistein, daidzein, and glycitein. The structure of the isoflavone molecule resembles that of many estrogenic and antiestrogenic compounds, including the physiologic estrogen 17β -estradiol and the synthetic selective estrogen receptor modulator tamoxifen. Therefore, isoflavone may have estrogenic or antiestrogenic activities depending on the target tissue [15,16].

Isoflavones have a common phenolic structure that seems to be a prerequisite for binding to estrogen receptors. These phytoestrogens, mainly genistein, seem to have more binding affinity for estrogen receptor β than for α ; therefore, showing tissue-selective effect, given the different tissue distribution of these α and β receptors [17]. Also, isoflavones have potentially important non-hormonal effects [16,18].

Isoflavones may be antagonist on the estrogenic receptor (ER) in uterine and breast tissues [19,20]. Alternatively, isoflavones may combine with the ER, albeit with lower affinity than 17β -estradiol [21], and stimulate estrogen activity, thus having an estrogenic effect on bone [19] and blood vessels [22].

Although conflicting results have been reported, some clinical studies confirm the health benefits by soy derivatives for menopause related conditions [23–28]. Data are often conflicting and difficult to analyze due to participant metabolic profile at baseline, large heterogeneity of soy derivatives used, duration of exposure and study design. To minimize this potential source of

bias, a standardized soy extract with 40% isoflavones was prepared in capsule form.

Previous work of our group has shown a significant improvement in menopausal symptoms in women taking isoflavone pills compared to placebo [24]. In addition, because estrogen therapy has been the most effective treatment for menopausal disturbance, we decided to compare the isoflavone effects on postmenopausal symptoms with the effects of mestrogen therapy.

2. Subjects and methods

2.1. Study design and treatment

This study was a single-center, 6-month, randomized, double-blind, estrogen-controlled trial designed to investigate the effects of 120 mg isoflavones per day (S40/Ach-1, Aché, São Paulo, Brazil) on menopausal symptoms, vaginal pH, vaginal cytology and endometrium (evaluated by ultrasound and biopsy). The Institutional Review Board of the Federal University of São Paulo approved the study and all participants signed an informed consent form at the beginning of the study. The study was conducted from July 2001 to November 2002.

After a pre-study period, 79 women were randomly assigned to one of the two treatment groups.

Isoflavone group: 300 mg of the standardized soy extract with a medium dose of 120 mg isoflavones/day, administered as capsules twice a day, each one containing 150 mg of soy extract with 60 mg isoflavones (daidzein isomers 20%, genistein isomers 75% and glycitein isomers 5%). The ratio between glycoside and aglycone forms is 0.61 (38% and 62% in each capsule, respectively).

Estrogen group: one capsule of 0.625 mg conjugated equine estrogens and other capsule with glucose 0.625 mg (placebo). In order to avoid bias in the double-blind design, conjugated equine estrogen were formulated in capsules.

All capsules had a similar appearance. The protocol required eight visits: two screening visits and six treatment visits (one visit per month).

2.2. Subjects

All subjects were recruited after an interview and health screen from the Climacterium Outpatient

Service at the Department of Gynecology of the Federal University of São Paulo/Escola Paulista de Medicina. All subjects included were postmenopausal women aged 45 years or older with good overall health, no menses for at least 12 months, follicle-stimulating hormone (FSH) levels of 30 mU/mL or more, intact uterus, echo endometrial thickness less than 5 mm and atrophic endometrium by biopsy. Exclusion criteria included strict vegetarian, high fiber, high soy diet, regular consumption of vitamin and mineral supplementation greater than the Recommended Dietary Allowances, antibiotic or hormone use within 6 months, history of chronic disorders including endocrine or gynaecological diseases or neoplasia, as well as benign breast disease, regular use of medication known to interfere with study endpoints and body mass index over 30. Also, patients with cervico-vaginal cytology classified as Class III of Papanicolaou or more. The subjects with hypertension could not use two or more antihypertensive drugs.

At the screening visit, 150 women responded to a standardized questionnaire, which ascertained information about demographic characteristics. Women were also queried about menopausal symptoms covered by the Kupperman Menopausal index [29], gynecologic history, including age at menopause, the use of selected medications, cigarette smoking history, frequency of alcohol use, physical activity, dietary and nutritional habits. Medication use was validated by examination of prescriptions or pills brought to the clinic for that purpose. The reasons of exclusion were presented in Table 1.

Table 1
The exclusion reasons of study

Reasons for exclusion	Number of patients
Endocrine disorders	11
BMI > 30	10
FSH < 30	9
Echo endometrial thickness > 5 mm	8
Hormonal drug user	8
Mammographic alteration	6
Pap smear alteration	6
Endometrium proliferative	5
Severe hypertension	4
Quit	4
Total	71

After fasting for 12 h, blood samples were obtained by venipuncture to measure FSH and 17 β -estradiol, that were measured by direct chemoluminescent assays (Advia Centauro, New York, USA). Height and weight were measured with subjects wearing lightweight clothing and no shoes; body mass index (calculated as kg/m²) was used as an estimate of obesity. Blood pressure was measured with a mercury sphygmomanometer after the subject had been seated quietly for at least 5 min.

During the gynecological exam, vaginal pH was measured. The pH paper (Merck 0-14, Darmstadt, Germany) was left for one minute in direct contact with one-third of external left vaginal wall. Vaginal cytology was performed using vaginal smears taken with vaginal spatulae from the right upper third of the vagina wall. The maturation of the vaginal epithelium was assessed manually, in Papanicolaou stained smears, by an experienced cytotechnologist and cytopathologist over 300 cells [30]. The maturation index was calculated as the percentage of parabasal, intermediate and superficial cells.

Transvaginal sonography was performed to evaluate the endometrial cavity, using a Toshiba SAL-38B real-time sonography fitted with a mechanical 5.0 MHz (Tochigi, Japan). Endometrial echo was measured in antero-posterior direction from the echogenic interface of the endometrium-myometrium junction on both sides in the thicker endometrial area in one-third of the uterine body [31]. After sonographical study, endometrial biopsy was performed using a Pipelle. The same pathologist performed all histopathological study.

The Kupperman index is a numerical conversion index including 11 menopausal symptoms: hot flushes (vasomotor), paresthesia, insomnia, nervousness, melancholia, vertigo, weakness, arthralgia or myalgia, headache, palpitations, and stinging. Each symptom on the Kupperman index was rated on a scale from 0 to 3 for no, slight, moderate, and severe complaints. To calculate the Kupperman index, the symptoms were weighted as follows: hot flashes (4 \times), paresthesia (2 \times), insomnia (2 \times), nervousness (2 \times), and all other symptoms (1 \times). The highest potential score is thus 51. The score of hot flushes was based on number of complaints per day: slight (more than 5), moderate [5–10], and severe (more than 10).

Patients were defined as “asymptomatic” regarding hot flushes when they had a zero score in Kupperman

Table 2
Measurements and tests performed at each visit

	Screening	1 month	2 months	3 months	4 months	5 months	6 months
Weight	X	X	X	X	X	X	X
Blood pressure	X	X	X	X	X	X	X
17 β -estradiol	X			X			X
FSH	X			X			X
pH vaginal	X			X			X
VC	X			X			X
TVUS	X			X			X
EB	X						X
Pap smear	X			X			X
Mammogram	X			X			X
Kupperman	X	X	X	X	X	X	X
Side effects		X	X	X	X	X	X

VC: vaginal cytology; TVUS: transvaginal ultrasound; EB: endometrial biopsy.

Menopausal Index question related to vasomotor symptoms. “Flush-ameliorated” was defined as any reduction in the score in Kuperman’s index question related to vasomotor symptoms.

After screening, 79 women were randomized using a software and submitted to the procedures in Table 2.

Safety evaluation was based on vital signs, pelvic and breast clinical exam, hematology, chemistry, Pap smear, endometrial thickness, endometrial biopsy, mammogram and report of adverse events.

Women were instructed to record the data they took study medication, as well as any dates they missed medication, on a daily dairy card, which they returned to the investigator at their next visit. The diary cards were also used to record adverse effects and bleeding information. To avoid compromising the double-blind design, the occurrence of side effects or physical changes such as bleeding, was recorded by an independent gynecologist.

2.3. Statistical considerations

Groups’ baseline data are presented in Table 4 with means and standard errors. These values were analyzed by Student’s *t*-test for independent samples to verify if there were differences between groups at study baseline. The comparison of categorical variables was done by the non-parametric Fisher’s exact test.

For vasomotor symptoms, FSH, 17 β -estradiol, vaginal pH and cytology, values obtained during the study for each treatment group were analyzed by one-way repeated measures analysis of variance, followed by

multiple comparisons Fisher’s test when a statistically significant difference was found. Comparisons between the two treatment groups at each timepoint during the study were done with Student’s *t*-test for independent samples.

An alpha error (*p*) level of 0.05 was used and an asterisk (*) indicates differences statistically significant. All statistical tests were done using Minitab® Release 13 Statistical Software for Windows® (Minitab Inc. State College, Pennsylvania USA). The power calculation ($1 - \beta$) for 0.8 was 23 patients per group.

3. Results

A total of 68 patients completed the 6-month treatment, 35 from estrogen group and 33 from isoflavone group. Only subjects who completed 6 months of treatment and took over 80% of their expected number drugs were included in the efficacy analysis. Table 3 shows the reasons and period of drop out from each group. One patient in isoflavone group had breast cancer that was diagnosed in the mammogram after 6 months of treatment. No serious adverse events related to isoflavone or estrogen treatments were reported.

The race distribution of the study sample was the following: 64%, 33% and 3% of women were white, black and Asian, respectively. Baseline characteristics of subjects are shown in Table 4. No significant differences were noticed among patients from the two treatment groups at baseline examination for age, blood pressure, body mass index, race, use of nicotine, age of

Table 3
The reasons and period of drop out from each group

Isoflavones (n = 7)		Estrogens (n = 4)	
Month	Reason	Month	Reason
First month	High values of tryglicerides	First month	Polymyositis
Second month	Moved out from São Paulo State	First month	Moved out from São Paulo State
Second month	Acute renal insufficiency	Second month	Quit
Fourth month	Depression	Sixth month	Panic of endometrial biopsy
Fourth month	Familiar problems		
Fifth month	Personal reasons		
Fifth month	Moved out from São Paulo State		

Comparison between isoflavone and estrogen groups ($p < 0.54$, unpaired Student's *t*-test).

menopause, time since last menses or physical activities.

3.1. Endogenous hormone

No differences were detected between isoflavone and estrogen treatment groups for FSH and 17 β -estradiol at baseline. There was a significant decrease in FSH levels in estrogen group after 3 and 6 months of treatment ($*p < 0.01$) compared to baseline and also compared with isoflavone group after 3 and 6 months. There were no significant changes in FSH levels in isoflavone group. Also, there was a statistical increase in 17 β -estradiol after 3 and 6 months of treatment

Table 4
Baseline characteristics of randomized subjects (mean and standard error)

	Estrogens (N = 35)	Isoflavones (N = 33)	<i>p</i>
Age (years)	53.7 \pm 0.9	53.9 \pm 0.9	0.88
BMI (kg/m ²)	25.6 \pm 0.6	25.5 \pm 0.7	0.95
Age at menarche (years)	13.2 \pm 0.5	13.5 \pm 0.5	0.66
Age at menopause (years)	46.8 \pm 0.9	48.6 \pm 0.8	0.14
Time since last menstrual period (years)	6.7 \pm 0.5	5.3 \pm 0.5	0.06
Physical activities (N)			0.34
No exercise	27	20	
Light	5	9	
Moderate	0	1	
Accentuate	3	2	
Cigarette user	7	11	0.27
Hypertension	5	8	0.76

p values reflect the results of Student's *t*-test for independent samples (for numeric variables) or Fisher's exact test (for categorical variables).

in estrogen group, compared both to baseline and isoflavone groups ($*p < 0.01$) (Fig. 1).

3.2. Menopausal symptoms

In order to evaluate menopausal symptoms, the menopausal Kupperman index questionnaire was applied. At baseline, menopausal symptom score was similar in both groups ($p = 0.46$). After 1 month, there was a significant decrease in symptomatology (total score) of 2.8 times ($*p < 0.001$ compared to baseline) in estrogen group and 1.8 times ($p < 0.01$ compared to baseline) in isoflavone group. There was also a significant improvement in symptomatology after the second month of treatment in the isoflavone group compared to the first month ($*p < 0.05$). After this period, the results were similar in both groups (Fig. 2).

The number of asymptomatic patients was 7 and 10 in isoflavone and estrogen groups, respectively. In order to evaluate hot flushes, only symptomatic patients were considered. The vasomotor symptoms at baseline were calculated following the Kupperman Menopausal Index: estrogen group 5.7 \pm 4.0 and isoflavone group 4.9 \pm 4.2 ($p = 0.46$, unpaired Student *t* test). There was a decrease in hot flushes after 1-month treatment in both groups. There was no difference between treatment groups at each timepoint during the study (Fig. 3).

3.3. Vaginal pH

There was no difference between the two treatment groups at baseline. In estrogen group, vaginal pH decreased significantly when compared with baseline mean 5.6–4.6 (after 3 months $*p < 0.01$) and 4.8

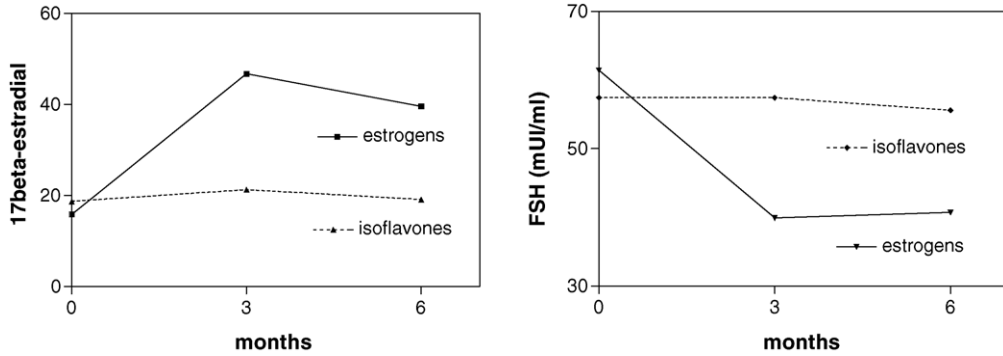


Fig. 1. 17β-estradiol and FSH mean levels in groups estrogens and isoflavones at baseline and after 3 and 6 months. 17β-Estradio levels in estrogen group: analysis of variance (ANOVA) for repeated measures: * $p < 0.0001$. Fisher’s multiple comparisons test: baseline, <3 months, and 6 months. 17β-Estradiol levels in isoflavone group: ANOVA for repeated measures: $p = 0.0042^*$. Comparisons of 17beta-estradio levels between estrogen and isoflavone groups (Student’s t -test for independent samples) 3 months, * $p = 0.024$; 6 months, * $p = 0.0042$. FSH levels in estrogen group: analysis of variance (ANOVA) for repeated measures: * $p < 0.0001$. Fisher’s multiple comparisons test: baseline, >3 months, and 6 months. FSH levels in isoflavone group: ANOVA for repeated measures: $p = 0.920$. Comparisons of FSH levels between estrogen and isoflavone groups (Student’s t -test for independent samples) 3 months, * $p = 0.0005$; 6 months, * $p = 0.0019$.

(after 6 months * $p < 0.01$). Results of estrogens group were also different when compared to the isoflavone group after 3 and 6 months. There was no difference in vaginal pH means in isoflavone group during treatment (Fig. 4).

3.4. Vaginal maturation index

Maturation index was similar in both groups at baseline. There was a statistically significant increase in intermediate and superficial cells frequency after 3 and 6 months of treatment in estrogen group when compared to baseline in the same group and also when compared to isoflavone group after 3 and 6 months. No differences were observed in isoflavone group during the trial (Fig. 5).

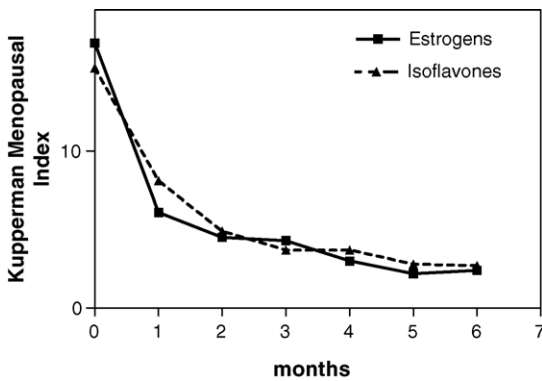


Fig. 2. Means of Kupperman Menopausal index score. Estrogen group: analysis of variance (ANOVA) for repeated measures: * $p < 0.0001$. Fisher’s multiple comparisons test: baseline, >1 month, =2 months, =3 months, =4 months, =5 months, and =6 months. Isoflavone group: analysis of variance (ANOVA) for repeated measures: * $p < 0.0001$. Fisher’s multiple comparisons test: baseline, >1 month, =2 months, =3 months, =4 months, =5 months, and =6 months. Comparisons of Kupperman Menopausal index between estrogen and isoflavone groups (Student’s t -test for independent samples): baseline, $p = 0.46$; 1 month $p = 0.23$; 2 months, $p = 0.75$; 3 months $p = 0.97$; 4 months, $p = 0.33$; 5 months $p = 0.49$; 6 months, $p = 0.74$.

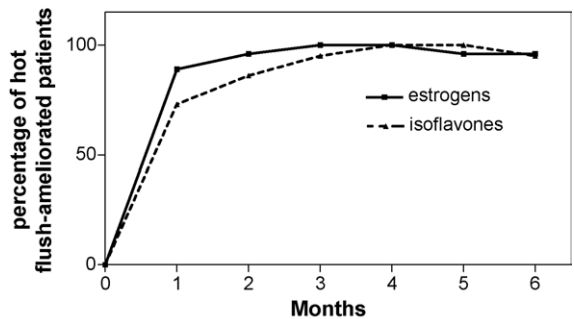


Fig. 3. Percentage of women that informed reduction in hot flushes of estrogen and isoflavone groups. Comparison between patients from estrogen (28) and isoflavone (22) groups that had hot flushes at the beginning of the trial. Student’s t -test for independent samples: 1 month, $p = 0.157$; 2 months, $p = 0.308$; 3 months, $p = 0.440$; 4 months, $p = 1.000$; 5 months, $p = 1.000$; 6 months, $p = 1.000$.

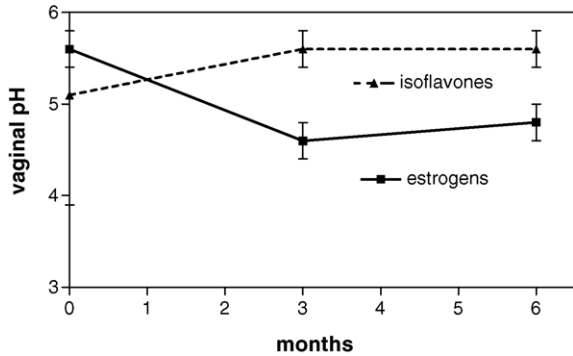


Fig. 4. Vaginal pH means of subjects in estrogen and isoflavone groups during treatment. pH in estrogen group: analysis of variance (ANOVA) for repeated measures: $p < 0.0001$. Fisher's multiple comparisons test: baseline, >3 months, and $=6$ months. pH in isoflavone group: ANOVA for repeated measures: $p = 0.095$. Comparisons of pH between estrogen and isoflavone groups (Student's *t*-test for independent samples) 3 months, $*p < 0.0001$; 6 months, $*p = 0.0012$.

3.5. Endometrium

Transvaginal ultrasound performed at baseline did not show significant difference between the two groups regarding mean endometrial thickness. Mean endometrial echo ranged from 2.8 to 6.2 mm (after 3 months) and to 5.9 (after 6 months) in the estrogen group, showing a statistically significant difference ($p < 0.01$) with baseline measures and also between treatment groups. Endometrial thickness did not change in the isoflavone group comparing each timepoint during

Table 5
Histopathological results of endometrial biopsy in the subjects (number of cases in each category)

Endometrium	Estrogens		Isoflavones	
	Baseline	6 months	Baseline	6 months
Atrophy	21	19	26	29
Proliferative	0	10	0	1
Hyperplasia	0	1	0	0
Insufficient tissue	14	5	7	3
Total	35	35	33	33

Fisher's exact test: estrogens group, comparison between baseline and 6 months: $p < 0.01$. Isoflavones group, comparison between baseline and 6 months: $p = 0.30$.

the study (mean baseline, 3.2 mm; after 6 months, 3.0 mm).

Endometrial biopsy results were similar at baseline in both groups. Endometrial pathology reports showed a significant higher prevalence of endometrial proliferation in the estrogen group either after treatment ($p < 0.01$) or compared to the isoflavone group at each timepoint during the study ($p < 0.01$). Endometrium was atrophic after treatment in the isoflavone group, except in one case (proliferative endometrium) (Table 5).

No side effects were detected in subjects who were receiving isoflavone, whereas in the estrogen group six patients reported genital bleeding.

After 6 months of treatment, one woman of isoflavone group presented signs of malignancy on mammography. Breast biopsy was performed and invasive ductal carcinoma diagnosed.

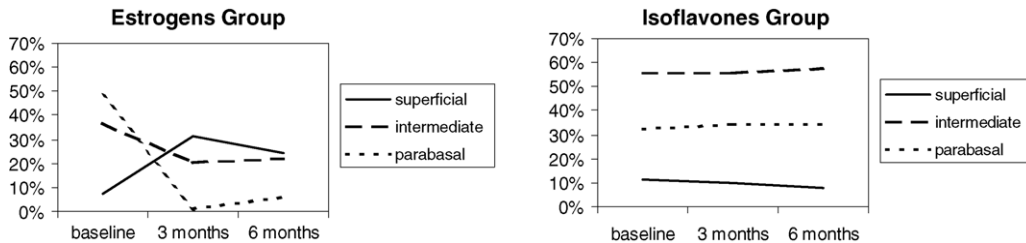


Fig. 5. Proportion of superficial, intermediate and parabasal cells in Pap smear in estrogen and isoflavone groups at baseline and after 3 and 6 months. Proportion of superficial cells in estrogen group: ANOVA for repeated measures: $*p < 0.0001$. Fisher's multiple comparisons test: baseline <3 months $=6$ months. Proportion of intermediate cells in estrogen group: ANOVA for repeated measures: $*p < 0.0001$. Fisher's multiple comparisons test: baseline, >3 months, and $=6$ months. Proportion of parabasal cells in estrogen group: analysis of variance (ANOVA) for repeated measures: $*p < 0.0001$. Fisher's multiple comparisons test: baseline, >3 months, and $=6$ months. Proportion of superficial cells in isoflavone group: ANOVA for repeated measures: $p = 0.361$. Proportion of intermediate cells in isoflavone group: ANOVA for repeated measures: $p = 0.974$. Proportion of parabasal cells in isoflavone group: ANOVA for repeated measures: $p = 0.972$.

4. Discussion

Epidemiological data and evidence from several human studies have shown that isoflavones might be an alternative therapy for postmenopausal climacteric symptoms. However, data are often conflicting, making difficult to conclude the real benefits of isoflavones.

The ideal dose of isoflavones required to obtain a clinical response may be questioned. The “normal” intake of isoflavone in a traditional Asian diet is 11–40 mg/day as aglycone or 18–63 mg/day as glycoside [32,33]. Results of a previous trial in our group used 100 mg/day [24].

Our trial showed that isoflavones 120 mg/day were effective in relieving menopausal symptoms. These results were consistent with previous studies that investigated isoflavone effect on hot flushes [23,25,26,28], although none of them compared isoflavone effects with estrogens. Conversely, other clinical trials have not observed an improvement in menopausal symptoms [34,35]. In addition, St. Germain et al. [35] found no treatment effects on change in hot flushes and night sweats frequency, whereas there was a significant decrease in hot flushes and night sweats frequency within time in the three treatment groups (isoflavone-rich soy protein, isoflavone-poor soy protein and whey protein control). The symptoms decrease was ascribed to either a placebo effect or a natural improvement in symptoms during the 24-week study.

Burke et al. [34] studied 241 peri- and postmenopausal women during two years. No significant differences in the number and severity of vasomotor symptoms were observed among the high isoflavone (58 mg/day), middle isoflavone (42 mg/day) or control groups (isoflavone extracted soy protein).

It is important to emphasize that some studies, such as St. Germain et al. [35] and Burke et al. [34] included perimenopausal women. Therefore, this fact may explain the negative results of those studies.

The real mechanism of isoflavone action is not known. One explanation might be the competition between isoflavones and estrogens for the receptors. Another one may be the initial low number of hot flushes per day in both studies compared to other trials in which beneficial effects were observed.

Also, it is difficult to evaluate subjective symptoms and their improvement with the treatment. There is a

large placebo effect and a natural improvement with time.

It is well known that the decrease in vaginal pH and the increase in superficial and intermediate cells are induced by estrogen therapy [30]. Our findings in the estrogen group are consistent with the literature. Although Dalais et al. [36] found a significant change in the vaginal cytology maturation index with soy, our study showed no change in vaginal pH or vaginal cytology in the isoflavone group. Also in Baird et al. [37], Murkies et al. [25], Scambia et al. [38] and Upmalis et al. [27] studies the vaginal cell maturation remained unchanged. These findings suggest that there are differences in the estrogenic effects of isoflavones that come from different sources, reinforcing the need to characterize each product separately.

Estrogen therapy has been reported to increase endometrial thickness and proliferate the endometrium [4]. Our study showed an effect on endometrium in the estrogen group that could be a risk factor for endometrial cancer. In the isoflavone group there was no significant effect in endometrium evaluated by ultrasound and biopsy, except one case of proliferative endometrium. This finding was in line with those of Scambia et al. [38], Upmalis et al. [27], Han et al. [24], that showed no increase in endometrial thickness by ultrasound. Foth and Cline [39] showed several potential mechanistic bases for antiproliferative effects of soy in primatal endometrium: high concentrations of serum sex hormone binding globulin and therefore less free estradiol in plasma, inhibition of aromatase activity and estradiol 17 β dehydrogenase, thus diminishing the formation of estradiol from other steroids.

Unfer et al. [40] reported that long-term treatment (up to 5 years) with soy phytoestrogens (150 mg of isoflavones per day) was associated with an increased occurrence of endometrial hyperplasia compared to placebo. One explanation for this effect is that phytoestrogens may act as a partial agonist on the ERs [41]. This fact may partially explain the case of proliferative endometrium found in our study.

This study supports the use of isoflavones for relief of menopausal symptoms. The absence of endometrial effects indicates that isoflavones from soy acts as a modified estrogen. Although the data do not support the use of isoflavones as an alternative to estrogen therapy in the prevention of long-term disease like osteoporosis, it may be safely and effectively used by women

who experience vasomotor symptoms and who choose not to take estrogens.

5. Conclusion

We concluded that the daily standardized soy extract with 120 mg isoflavones' effect on symptoms was similar to that from estrogen. Soy isoflavone is well tolerated and has no estrogenic effect on endometrium and vaginal mucosa during 6 months of treatment.

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