

## MENOPAUSE

# The effect of red clover isoflavones on menopausal symptoms, lipids and vaginal cytology in menopausal women: A randomized, double-blind, placebo-controlled study

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### Abstract

**Background.** The unexpected results of the Women's Health Initiative study have decreased the use of conventional hormone therapy (HT), changing physicians' and patients' attitudes towards HT and increasing their interest in alternative options.

**Objective.** The present study aimed to evaluate the effect of isoflavones contained in red clover extracts (*Trifolium pratense*) on menopausal symptoms, lipids and vaginal cytology in menopausal women.

**Methods.** Sixty postmenopausal women aged >40 years, non-users of HT, with Kupperman index score  $\geq 15$ , were double-blindly randomized to receive either a commercially available red clover isoflavone supplement (80 mg/day) or placebo for 90 days. Subsequently, after a 7-day washout period, subjects switched to receive the opposite treatment for a further 90 days. Kupperman index score was determined and fasting blood and vaginal cytologic sampling performed at baseline, 90 and 180 days.

**Results.** Fifty-three women (88.3%) completed the trial. Mean age was  $51.3 \pm 3.5$  years, 69.7% of the women were aged 50 years or more. There was no significant effect on body mass index, weight or blood pressure after either treatment phase. Baseline Kupperman index score decreased significantly after each treatment phase, with the decrease more pronounced after the isoflavone phase (baseline:  $27.2 \pm 7.7$ ; after isoflavone:  $5.9 \pm 3.9$ ; after placebo:  $20.9 \pm 5.3$ ,  $p < 0.05$ ). Red clover isoflavone supplementation significantly decreased the rate of menopausal symptoms and had a positive effect on vaginal cytology as expressed by improvement in karyopyknotic, cornification and basal cell maturation indices. Mean total cholesterol, low-density lipoprotein-cholesterol and triglyceride levels also decreased; however, only the latter was significantly lower compared with placebo.

**Conclusions.** Compared with placebo, red clover isoflavone supplementation in postmenopausal women significantly decreased menopausal symptoms and had a positive effect on vaginal cytology and triglyceride levels.

**Keywords:** Menopausal symptoms, isoflavones, phytoestrogens, red clover extracts

### Introduction

Median age of menopause varies in Latin America, but in general has been reported to occur earlier than among women in the USA and Europe, a fact that has been related to the altitude of the geographical zone and the lower educational and socioeconomic level of its inhabitants [1–4]. In this sense, high intensity of climacteric symptoms has been reported among low-income Ecuadorian women [5]. Quality of life for Latin American women is a direct consequence of the age of menopause and the intensity of symptoms.

Women worldwide have received benefit from hormone therapy (HT) for alleviation of the climacteric syndrome and the prevention of osteoporosis and other age-related conditions [6–9]. Despite this,

compliance in developed and non-developed countries is low. Factors contributing to this low compliance have been reported as side-effects, implicated costs, poverty, poor health coverage and the fear of developing cancer [10–12]. With regard to the latter, HT use has further decreased after the unexpected findings of the Women's Health Initiative (WHI) study in which one HT regimen significantly increased the risk for cardiovascular events and breast cancer [13]. In Chile, the use of HT decreased significantly 3 months following publication of the results of the WHI trial, indicating physicians' and patients' changing attitudes towards HT [14]. Therefore an ideal HT regimen should cost-effectively treat climacteric symptoms, produce the least side-effects, be accepted and easily managed by the medical

community and lack the need for sophisticated follow-up.

The surprising results of the WHI study have increased research seeking for newer hormonal compounds that may influence key target organs effectively, selectively and in a physiological manner [15]. Although this ideal treatment does not exist, phytoestrogens approach this clinical profile. They are plant-derived molecules, mainly represented by isoflavones, that exhibit estrogenic effects [16,17]. Although less potent than conventional estrogenic compounds, their selective binding to the  $\beta$  estrogenic receptor (ER $\beta$ ) allows a positive effect on bone, vagina, brain and the cardiovascular system with no effect on the uterus and breast, thus making them an excellent alternative HT option, especially for high-risk women and those with poor compliance [18–20]. Although alternative menopausal therapeutic research has mostly focused on soy-derived isoflavones, the use of other plant-derived products (red clover extracts, *Cimicifuga racemosa*, kava, dong quai, burdock, etc.) has increased significantly [21]. Interest in isoflavones derived from red clover extracts (*Trifolium pratense*), a type of phytoestrogen, is increasing among women and researchers, and their positive effects have been reported [22–25]. Despite this, data provided from clinical trials in Latin America are still scarce [26].

The objective of the present research was to evaluate the effect of isoflavones contained in red clover extracts (*T. pratense*) on menopausal symptoms, lipids and vaginal cytology in menopausal women.

## Materials and methods

### Subjects

This prospective, randomized, double-blind, placebo-controlled trial was carried out by the Foundation for Health and Well Being in the Climacteric ('FUCLIM') of Guayaquil, Ecuador, a non-profit organization that provides free health care for climacteric women, especially of low income, through the private practice of institutional members (authors included) and the Institute of Biomedicine of the Catholic University of Santiago de Guayaquil. The study protocol was approved by the Medical Faculty Institutional Review Board and Ethics Committee.

Sixty postmenopausal women (amenorrhea > 12 months) over 40 years of age, non-users of HT, with moderate to severe menopausal symptoms (Kupperman index score  $\geq 15$ , basal determination), were recruited from the foundation's clinical database, investigators' private practice or from the general population through newspaper advertising and flyers posted at the university campus. Women expressing interest in participating were set up for an initial visit with one of the investigators, during which the study was explained in detail, sociodemographic data recorded and those wishing to participate were asked for written informed consent. Body mass index (BMI),

Kupperman index scores and blood pressure determinations were recorded at baseline, 90 and 180 days. Blood and vaginal cytologic samples were also obtained at equal intervals. Women not consenting to participate, not expressing their willingness to take the prescribed preparations and adhere to the control dates, as well as those on conventional HT, isoflavone-derived supplements, thyroid medication (or history of thyroid disease) or on medication that could interfere with vasomotor symptoms and/or lipid serum levels were excluded. BMI was calculated as [weight (kg)/square of height (m)] [27]. Blood pressure determinations were performed after women had been sitting for 15 min, those having values  $\geq 140/90$  mmHg or already on antihypertensive drugs were defined as having hypertension [28]. Women on hypoglycemic drugs indicated by a physician were considered diabetic.

### Assignment

After obtaining signed consent, participants were assigned by computerized random number generation to initiate daily either two capsules of red clover isoflavone supplement or placebo for a 90-day period. Subsequently, after a 7-day washout period, subjects switched to receive the opposite treatment for a further 90 days (net trial duration 180 days in total). Melbrosin International (Vienna, Austria) provided identically manufactured placebo and red clover isoflavone capsules placed in opaque containers (60 capsules each) labeled as A or B; investigators and participants were blinded to the contents until the end of the trial, after which the code was broken. Each capsule of red clover supplement provided approximately 40 mg isoflavones (Menoflavon<sup>®</sup>; Melbrosin International).

### Kupperman index

The Kupperman index assessed the severity of 11 menopausal symptoms occurring over the past 4 weeks. Symptoms included within this scale were: hot flushes, nocturnal sweating, sleeping disorders, nervousness, depression, dizziness, lack of concentration, arthralgia, headaches, palpitations and vaginal dryness [29]. Each subject scored the particular symptom as: 0 = not present; mild = 1; modest = 2; and severe = 3. Total Kupperman index score for a given subject was the sum of each individual symptom score. Dyspareunia and decreased libido were also evaluated, although not considered part of Kupperman index scoring.

### Vaginal sampling

Using sterile speculum examination, vaginal cytologic smears were obtained for evaluation of the percentage of squamous cells with nucleic picnosis (karyopyknotic index), percentage of squamous cells

with cytoplasmic acidophilia (cornification index) and the percentage of basal, intermediate and superficial cells (maturation index) [30].

#### Blood samples

A 15–20 ml fasting blood sample was withdrawn from each participant at the planned intervals. After centrifugation for 10 min at 3000 rev/min and 5°C, serum was decanted into 1.5 and 2.0 ml aliquots and stored at –70°C at the Institute of Biomedicine until further analysis for total cholesterol (TC), triglycerides (TG), low-density lipoprotein-cholesterol (LDL-C), high-density lipoprotein-cholesterol (HDL-C), lipoprotein A (LpA), follicle-stimulating hormone (FSH), luteinizing hormone (LH), 17 $\beta$ -estradiol (E<sub>2</sub>), sex hormone-binding globulin (SHBG) and testosterone (T). TC, TG, LDL-C, HDL-C and LpA were assayed with a Hitachi 717 automatic photometric analyzer (Roche Diagnostics, GmbH, Mannheim, Germany). FSH, LH, E<sub>2</sub>, T and SHBG were assayed with an Immulite 2000 automatic immunoanalyzer using the chemiluminiscent technique (Diagnostics Products Corporation, Los Angeles, CA, USA). A cut-off value FSH > 30 mIU/ml on basal determination was confirmatory of postmenopausal status [24].

#### Statistical analysis

Assuming that red clover isoflavone supplementation would reduce the percentage of women presenting hot flushes by 44% as determined by others [22], it was calculated that a sample size of 88 subjects (44 on each arm) would be required to achieve 90% power with 95% confidence level (5% alpha risk). Data analysis was performed using EPI-INFO 2000 statistical software (Centers for Disease Control and Prevention, Atlanta, GA, USA/World Health Organization, Geneva, Switzerland). Data are presented as mean  $\pm$  standard deviation, mean differences, confidence intervals and percentages. Individual menopausal symptom scores were dichotomized as present or absent and presented as percentages. Comparison of continuous and categorical data was performed with the paired Student *t* test and the  $\chi^2$  test, respectively. A *p* value < 0.05 was considered as significant. Women abandoning the trial were not included in the final statistical analysis.

#### Results

Sixty postmenopausal women were enrolled in this double-blind, randomized, placebo-controlled study performed from July 2003 to August 2004. Seven subjects (11.7%) did not complete the trial and therefore were excluded from the analysis: five abandoned treatment for no specified reasons and two because of side-effects (headache; one woman during the placebo phase and the other during the isoflavone supplementation phase). Mean age (*n* = 53:

88.3%) was 51.3  $\pm$  3.5 years, 69.7% of the women were aged 50 years or more and 5.7% were diabetic, had hypertension or a history of hysterectomy. Women were married in 43.4% of cases and had an educational level < 12 years or were non-professionals in 54.7% and 73.6% of cases, respectively.

The effect of each phase of the trial on weight, blood pressure, Kupperman index score and vaginal cytology is presented in Table I. There was no significant effect on baseline BMI, weight and blood pressure after completing either trial phase. Baseline Kupperman index score decreased significantly after each trial phase, the decrease being more pronounced after the isoflavone phase (baseline: 27.2  $\pm$  7.7; after isoflavone supplementation: 5.9  $\pm$  3.9; after placebo: 20.9  $\pm$  5.3, *p* < 0.05). Red clover isoflavone supplementation had a positive effect on vaginal cytology as evidenced by improvement in karyopyknotic, cornification and basal cell maturation indices (Table I and Figure 1). All menopausal symptoms assessed with the Kupperman index (expressed as percentages), as well as the percentage of women with dyspareunia libido, decreased significantly after supplementation with red clover isoflavones and returned similar baseline values after completion of the placebo phase (Figure 2).

Lipid and hormonal profile after each phase of the trial is shown in Table II. Red clover isoflavone supplementation significantly decreased basal TC, LDL-C and TG levels. However, only the decrease in TG was also significantly lower compared with levels after the placebo phase. Serum LpA levels decreased significantly after both treatment phases. Although T levels decreased significantly after red clover supplementation, there were no significant changes in FSH, LH and E<sub>2</sub> levels with either treatment phase.

#### Discussion

Although the climacteric has not been studied extensively in Latin America, evidence indicates that the menopause occurs earlier there than in other populations, exposing women to the negative effects of a low estrogen milieu with its concomitant adverse impact on quality of life. Although the benefits of HT are undeniable [6–9], compliance in developed and non-developed countries is relatively low [10–12]. Furthermore, its use decreased after the unexpected findings of the WHI trial [13]. Although the results of this trial may be applicable to only one hormonal regimen, there is evidence of an overall decreasing trend in HT use regardless of the hormonal compound and regimen involved [14]. Under this new scenario, an ideal HT regimen should be cost-effective, produce few side-effects, be easy to manage and have selective action over targeted organs needed to meet physiological needs. Interest in isoflavones present in soy compounds and in red clover extracts (*T. pratense*) is increasing among women and practitioners, and their positive effects are currently

Table I. The effect of red clover isoflavone supplementation on weight, blood pressure, menopausal symptoms and vaginal cytology in menopausal women.

Parameter	Baseline (n = 53)	After isoflavone supplementation (n = 53)	After placebo (n = 53)
Systolic blood pressure (mmHg)	118.3 ± 13.3	117.2 ± 12.8	119.2 ± 12.8
Mean change <sup>†</sup>		(0.3; 8; -1.8, 2.6) <sup>a</sup>	(-0.8; 7; -2.8, 1.0) <sup>b</sup>
Diastolic blood pressure (mmHg)	76.6 ± 10.7	76.2 ± 10.2	76.6 ± 9.6
Mean change		(0.4; 7; -1.5, 2.3) <sup>a</sup>	(0.4; 7.6; -2, 2) <sup>b</sup>
Weight (kg)	64.2 ± 11.2	64.3 ± 11.3	64.7 ± 11.9
Mean change		(0.1; 2; -0.6, 0.5) <sup>a</sup>	(-0.4; 1.9; -1.0, 0.05) <sup>b</sup>
Body mass index (kg/m <sup>2</sup> )	26.6 ± 3.9	26.6 ± 3.9	26.8 ± 4.2
Mean change		(0; 0.8; -0.2, 0.2) <sup>a</sup>	(-0.2; 0.8; -0.4, 0.03) <sup>b</sup>
Kupperman index (total score)	27.2 ± 7.7	5.9 ± 3.9	20.9 ± 5.3
Mean change		(21.3; 8; 19.0, 23.5) <sup>a*</sup>	(6.3; 7.3; 4.3, 8.3) <sup>a*</sup> (-14.5; 6.5; -16.7, -13.1) <sup>b*</sup>
<i>Vaginal cytology</i>			
Karyopyknotic index (%)	6.1 ± 11.7	45.6 ± 27.4	3.6 ± 7.6
Mean change		(-39.5; 26.5; -46.8, -32.2) <sup>a*</sup>	(42; 28.2; 34.3, 49.8) <sup>b*</sup>
Cornification index (%)	6.1 ± 11.6	45.7 ± 26.0	3.9 ± 8.8
Mean change		(-39.6; 25.3; -46.6, -32.7) <sup>a*</sup>	(41.3; 27.1; 34.3, 49.3) <sup>b*</sup>
Parabasal cells (%)	68.4 ± 36.7	1.9 ± 12.7	65.2 ± 37.4
Mean change		(66.4; 37.7; 56.0, 76.9) <sup>a*</sup>	(-63.2; 37.8; -73.6, -52.8) <sup>b*</sup>
Intermediate cells (%)	27.4 ± 32.5	39.6 ± 25.4	30.2 ± 31.9
Mean change		(-12.2; 38.7; -22.9, -1.5) <sup>a*</sup>	(9.4; 35.8; -0.5, 19.3) <sup>b</sup>
Superficial cells (%)	4.2 ± 7.8	57.9 ± 25.9	4.7 ± 9.8
Mean change		(-53.8; 24.7; -60.6, -47.0) <sup>a*</sup>	(53.2; 28.5; 45.4, 61.0) <sup>b*</sup>

\*Mean change was significantly different (<sup>a</sup>vs. baseline, <sup>b</sup>vs. red clover phase).  $p < 0.05$ ; <sup>†</sup>values in parentheses are (mean difference; standard deviation; 95% confidence interval).

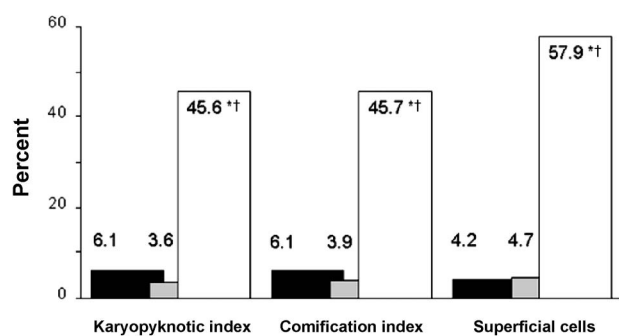


Figure 1. Vaginal cytology at baseline (black bars), after placebo (gray bars) and after supplementation with red clover isoflavones (white bars). Data given are means. \*Mean value was significantly different compared to baseline and placebo ( $p < 0.05$ ).

being supported by a growing body of evidence-based clinical research [22,23,31–36]. Despite this, an inconvenience of phytoestrogen use is the low level of knowledge about their biology and pharmacological beneficial properties. This is especially true in Latin America, where data provided from clinical trials regarding their use is scarce or non-existent [26]. The present research, to the best of our knowledge unique of its kind in Latin America, was designed to evaluate the effects of red clover isoflavones in menopausal women and provide clinical data drawn upon a Latin American population.

Retrospective studies have shown an inverse relationship between the dose of isoflavones consumed and the rate of hot flashes. Despite this, prospective trials studying the effect on vasomotor symptoms of using soy or red clover isoflavone compounds have produced conflicting results, imposing interpretation difficulties. For instance, while some studies have described a null effect on vasomotor symptoms with soy [37–39] or red clover compounds [40,41], others have also described symptom improvement with soy [42–44] and red clover-derived products [22,26].

Red clover extracts are often referred to as being better than other plant extracts as sources of phytoestrogens, largely due to the development of effective standardization of the isoflavone extraction process, so that reliable compositions of the medication can be obtained. Moreover, the isoflavones contained in red clover extracts are deemed to possess higher potential estrogenic activity, due to transformation toward more active compounds throughout intestinal absorption [18,45].

Supplementation with red clover isoflavones in the present study significantly decreased baseline Kupperman index score and the rate of menopausal symptoms expressed as percentages, supporting the findings of others. Contrary to this, in the recently published Isoflavone Clover Extract Study, two dietary supplements derived from red clover failed to reduce hot flashes in postmenopausal women

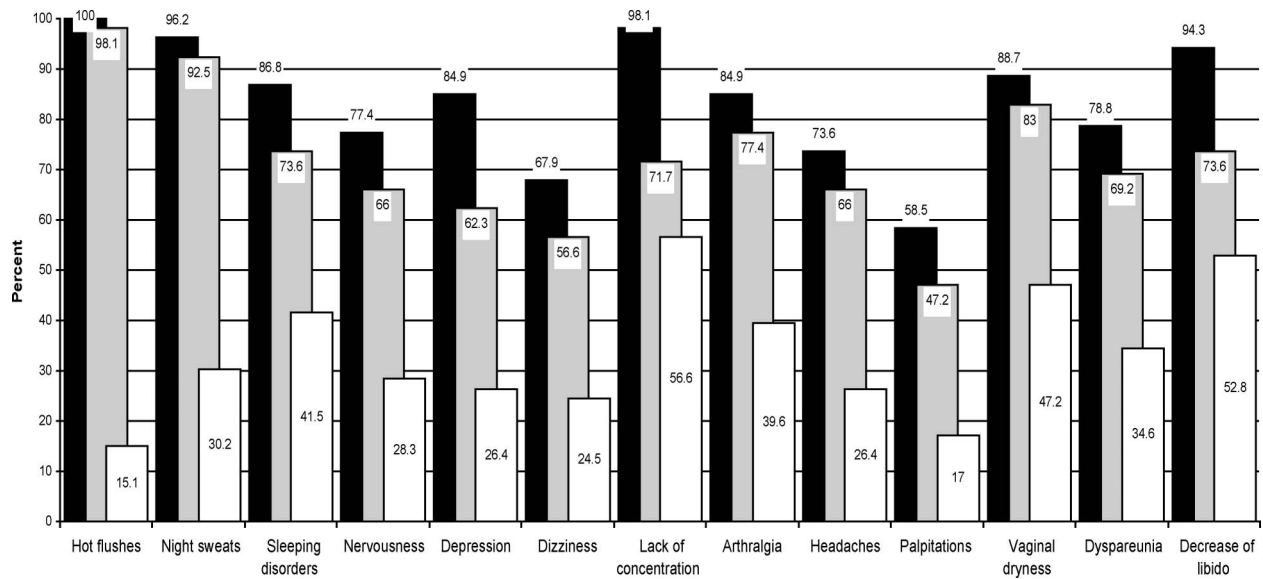


Figure 2. Frequency of menopausal symptoms (%) at baseline (black bars), after placebo (gray bars) and after supplementation with red clover isoflavones (white bars). All symptoms decreased significantly after the red clover phase compared with baseline and placebo ( $p < 0.05$ ).

Table II. The effect of red clover isoflavone supplementation on serum biochemical parameters in menopausal women.

Parameter	Baseline ( $n = 53$ )	After isoflavone supplementation ( $n = 53$ )	After placebo ( $n = 53$ )
Total cholesterol (mg/dl)	223.9 $\pm$ 37.6	214 $\pm$ 32.2	220.4 $\pm$ 34.1
Mean change <sup>†</sup>		(9.8; 33.0; 0.7, 18.9) <sup>a*</sup>	(-6.3; 32.9; -15.4, 2.7) <sup>b</sup>
High-density lipoprotein-cholesterol (mg/dl)	39.7 $\pm$ 11.5	40.0 $\pm$ 9.6	41.1 $\pm$ 10.0
Mean change		(-0.3; 8.7; -2.7, 2.1) <sup>a</sup>	(-1.1; 9.8; -3.8, 1.5) <sup>b</sup>
Low-density lipoprotein-cholesterol (mg/dl)	146.8 $\pm$ 29.9	129.7 $\pm$ 39.4	140.0 $\pm$ 35.2
Mean change		(17.0; 39.5; 6.1, 27.9) <sup>a*</sup>	(-1.1; 9.8; -3.8, 1.5) <sup>b</sup>
Triglycerides (mg/dl)	199.6 $\pm$ 77.8	181.1 $\pm$ 72.3	242.7 $\pm$ 166.9
Mean change		(18.5; 77.5; -2.8, 39.8) <sup>a*</sup>	(-61.5; 148.9; -102.5, -20.5) <sup>b*</sup>
Lipoprotein A (mg/dl)	41.2 $\pm$ 36.9	22.8 $\pm$ 26.9	20.5 $\pm$ 25.8
Mean change		(18.4; 43.7; 6.3, 30.4) <sup>a*</sup>	(2.3; 29.0; -5.7, 10.3) <sup>b</sup>
Sex hormone-binding globulin (nmol/l)	50.1 $\pm$ 23.7	46.9 $\pm$ 21.9	49.0 $\pm$ 22.0
Mean change		(3.1; 19.1; -2.1, 8.4) <sup>a</sup>	(-2.0; 20.2; -7.6, 3.5) <sup>b</sup>
Follicle-stimulating hormone (mIU/ml)	63.7 $\pm$ 22.6	63.3 $\pm$ 26.1	62.6 $\pm$ 22.1
Mean change		(0.5; 16.8; -4.1, 5.1) <sup>a</sup>	(0.7; 16.0; -3.7, 5.1) <sup>b</sup>
Luteinizing hormone (mIU/ml)	27.7 $\pm$ 13.8	30.8 $\pm$ 13.4	28.7 $\pm$ 14.0
Mean change		(-3.0; 11.7; -6.3, 0.2) <sup>a</sup>	(2.0; 12.4; -1.3, 5.4) <sup>b</sup>
17 $\beta$ -Estradiol (pg/ml)	23.8 $\pm$ 8.8	22.4 $\pm$ 7.2	20.9 $\pm$ 4.6
Mean change		(1.3; 9.2; -1.2, 3.8) <sup>a</sup>	(1.5; 9.0; -1.0, 4.0) <sup>b</sup>
Testosterone (ng/dl)	24.8 $\pm$ 11.2	21.4 $\pm$ 5.0	23.2 $\pm$ 11.3
Mean change		(3.4; 11.4; 0.3, 6.5) <sup>a*</sup>	(-1.7; 12.2; -5.1, 1.6) <sup>b</sup>

\*Mean change was significantly different (<sup>a</sup>vs. baseline, <sup>b</sup>vs. red clover phase).  $p < 0.05$ ; <sup>†</sup>values in parentheses are (mean difference; standard deviation; 95% confidence interval).

[46]. The positive effect of isoflavones on hot flushes has been hypothesized to be through an agonistic estrogenic effect on the hypothalamic thermoregulating center. One study using red clover-derived isoflavones demonstrated that the disappearance of hot flushes was directly correlated with the decrease in serum FSH levels [26]. Despite the positive effect on hot flushes found in the present study, a placebo effect cannot be ruled out as there were no significant differences in FSH levels after completing either treatment phase. Future research is warranted in this regard, to further explore the intrinsic mechanism of action of red clover isoflavones on the thermoregulating center.

Although data regarding the effect of soy isoflavones on the vaginal epithelium are conflicting, some indicating it to be positive [47] and others not [48–50], to best of our knowledge no study has reported the effect of red clover isoflavones on the vaginal epithelium. In the present trial, supplementation with red clover isoflavone extracts had a positive estrogenic effect on the vagina, increasing cellular mitotic activity as evidenced by improvements in karyopyknotic, cornification and basal cell maturation indices. These findings correlated well with the overall decrease in the rate of dyspareunia.

Evidence in the literature assessing the possible benefit of phytoestrogens in cardiovascular risk is

growing, and could be related to lipid profile modification, antioxidant activity, inhibition of platelet aggregation and their direct effect over the vascular endothelium [51,52]. Recent prospective observational studies demonstrated that arterial stiffness is predictive of future cardiovascular events and that progression of arterial stiffness is associated with increased cardiovascular mortality [53,54]. In this regard, red clover isoflavone supplementation has shown to improve arterial compliance [55], reducing stiffness [56] and exerting a positive effect on blood pressure [57]. These positive vascular effects have been correlated with recent *in vitro* studies [58,59] showing that soy and red clover isoflavones directly modulate human endothelial cells, triggering nitric oxide synthesis through ER $\beta$  activation which in turn induce potentially important vascular anti-inflammatory and antiatherogenic effects.

Supplementation with phytoestrogens decreases LDL-C, upgrading liver LDL receptors and decreasing endogenous cholesterol production through inhibition of 7 $\alpha$ -hydroxylase [60], although no conclusive evidence regarding the effect of red clover isoflavones on lipid profile has been published to date. Relevant observations include an increase in HDL-C and a decrease in apolipoprotein B and TG levels in postmenopausal women [23,24] and a decrease in LDL-C levels in men [61]. Some of these findings correlate with those of the present research, as red clover isoflavone supplementation significantly decreased mean baseline cholesterol, LDL-C and TG levels, representing a 4.4%, 11.5% and 9.5% drop from baseline, respectively. However, this was more evident for TG levels which, after red clover supplementation, decreased significantly compared with baseline and the placebo phase. These changes in general correlate with the findings of others and support the fact that minimal changes in the lipid profile could potentially be associated with an important reduction in cardiovascular risk [24], all the more in postmenopausal women with high lipid values. Schult and colleagues [24] found that the effect of red clover supplementation was most significant in women with high baseline TG values, a fact that supports our findings with regard to serum TG level which at baseline was 199.6 mg/dl.

Although these findings on lipid profile may seem promising, no definitive conclusion may be drawn. However, to reduce conflicting results in future research investigating the effects of red clover supplementation in postmenopausal women, several aspects should be taken into account:

- (1) Individualization of women to be treated for the assessment of a specific outcome (i.e., hormonal status, baseline lipid levels, bone status, individual dietary and nutritional habits, etc.).
- (2) Standardization of the compound to be used.
- (3) Individual differences with regard to absorption and metabolism [63].

In conclusion, the present study found that, compared with placebo, red clover isoflavone supplementation in postmenopausal women significantly decreased menopausal symptoms and had a positive effect on vaginal cytology and TG levels.

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