

## Soy-isoflavone supplementation tends to reduce menopausal symptoms in postmenopausal women

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### ABSTRACT

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#### BACKGROUND

Menopausal symptoms in postmenopausal women tend to decrease health-related quality of life (HRQoL). The present study's objective was to determine the effect of daily supplementation of 100 mg soy isoflavones on menopausal symptoms of healthy postmenopausal women. Isoflavones are phytoestrogens abundantly found in soy beans, and several studies have demonstrated that isoflavones are the best among the phytoestrogens.

#### METHODS

The study was a community-based double blind randomized controlled trial involving 60 healthy postmenopausal women, aged between 48–60 years, in the Mampang Prapatan District, South Jakarta. Participants were block-randomized to receive either 100 mg soy-isoflavone + 500 mg calcium carbonate (intervention group) or 500 mg calcium carbonate only (control group). Both supplements were taken daily for 12 weeks, from January to April 2010. Menopausal symptoms (measured by Menopause Rating Scale questionnaire) were assessed at baseline and after supplementation. Chi-square test was used to examine the effect of soy isoflavone supplementation on menopausal symptoms.

#### RESULTS

Fifty-six (93.3%) of participants completed the study. There were no statistically significant differences ( $p>0.05$ ) in the prevalence of menopausal symptoms between the isoflavone group and the control group. However, supplementation of soy isoflavones for 12 weeks tended to decrease the prevalence of menopausal symptoms in women with normal body mass index and adequate daily dietary isoflavone intake.

#### CONCLUSION

Daily supplementation of 100 mg soy isoflavones for 12 weeks tend to decrease the incidence of menopausal symptoms in postmenopausal women.

**Key words :** Soy isoflavones, menopausal symptoms, postmenopausal

## ***Suplementasi soy isoflavon cenderung meringankan simtom menopause pada perempuan pascamenopause***

### **ABSTRAK**

#### **LATAR BELAKANG**

Simtom menopause yang berkaitan dengan penurunan kadar estrogen dapat menurunkan kualitas hidup yang berkaitan dengan kesehatan (health-related quality of life) perempuan pascamenopause. Penelitian ini bertujuan untuk menilai pengaruh suplementasi harian soy-isoflavon 100 mg terhadap simtom menopause pada perempuan pascamenopause yang sehat. Isoflavon merupakan salah satu jenis fitoestrogen, dan beberapa penelitian menunjukkan bahwa isoflavon merupakan jenis fitoestrogen yang terbaik, banyak ditemukan dalam kedelai (soy) yang banyak dikonsumsi oleh masyarakat Indonesia dan penduduk Asia lainnya.

#### **METODE**

Rancangan community-based double blind randomized controlled trial yang digunakan melibatkan 60 perempuan pascamenopause berusia antara 48–60 tahun di Kecamatan Mampang Prapatan – Jakarta Selatan. Subyek penelitian secara randomisasi blok dibagi menjadi kelompok yang mendapat suplemen soy-isoflavon 100 mg + kalsium karbonat 500 mg dan yang mendapat kalsium 500 mg karbonat saja selama 12 minggu, yaitu antara Januari dan April 2010. Penilaian simtom menopause dilakukan dengan menggunakan kuesioner Menopause Rating Scale (MRS) terhadap subyek penelitian sebelum dan sesudah suplementasi. Analisis statistik yang digunakan adalah uji chi-square.

#### **HASIL**

Sebanyak 56 subyek (93,3%) menyelesaikan penelitian ini. Tidak ada perbedaan yang bermakna secara statistik ( $p > 0,05$ ) dalam hal kejadian simtom menopause (gangguan psikologik, vasomotor dan urogenital) antara kelompok subyek yang mendapatkan isoflavon dan kelompok kontrol, tapi pemberian suplementasi isoflavon cenderung menurunkan angka kejadian simtom menopause pada perempuan pascamenopause dengan indeks massa tubuh yang normal dan asupan isoflavon dalam makanan harian yang cukup.

#### **KESIMPULAN**

Suplementasi 100 mg soy-isoflavon selama 12 minggu cenderung menurunkan angka kejadian simtom menopause pada perempuan pascamenopause.

**Kata kunci :** Soy-isoflavon, simtom menopause, pascamenopause

## **INTRODUCTION**

The decrease in sex hormone levels in the body, in particular estrogens, as occurs in menopausal women, not only changes the menstrual pattern but also impacts on general health. These health changes comprise mainly somatic, urogenital and vasomotor symptoms, such as loss of skin elasticity leading to a

wrinkled appearance of the skin, dryness of the vagina (causing dyspareunia), dysuria, palpitations, migraine, hot flushes [or hot flashes], nocturnal sweats, insomnia, and sexual symptoms, the whole being known as the menopausal symptoms.<sup>(1)</sup>

The prevalence of menopausal symptoms in European and American women is up to 50-75%, whereas in Asian women it is only around

20-25%.<sup>(2)</sup> The prevalences of vasomotor symptoms in Indonesia among premenopausal, perimenopausal and postmenopausal women are 6%, 30%, and 8%, respectively.<sup>(3)</sup>

Hormone therapy (HT), in the form of estrogens only or in combination with progestones, has in the last few years still been the most prescribed treatment for postmenopausal women in industrialized countries.<sup>(4)</sup> Administration of HT forms part of several measures to attain and maintain quality of life in menopausal women. There is a considerable body of evidence regarding the beneficial effects of HT on menopausal symptoms, lipid profile, osteoporosis, dementia and colorectal cancer. Most women use HT to relieve menopausal symptoms and to prevent chronic disease, such as osteoporosis, coronary heart disease (CHD) and Alzheimer's dementia. On the basis of recommendations issued by the North American Menopause Society (NAMS), the indications for HT administration are the various menopausal symptoms, such as vasomotor and urogenital symptoms.<sup>(4)</sup>

As with other medications, in addition to its many beneficial effects, HT may cause various adverse reactions, from mild (nausea, mastalgia, headaches) to severe (uterine bleeding). Studies have associated the use of HT with increased risk of several diseases, such as coronary heart disease, venous thromboembolism (VTE) and ovarian malignancies.<sup>(5)</sup> The use of HT in Asia is still very limited and HT is given only to menopausal patients with complaints related to troublesome estrogen deficiency, or to the hazard of osteoporosis and fractures.<sup>(6)</sup>

The Women's Health Initiative Randomized Trial reported on the increased risk of breast cancer, coronary heart disease, stroke and venous thromboembolism (VTE) in users of HT. This has caused some women to refuse using HT and to look for alternative treatments capable of fulfilling their need for alleviation of menopausal symptoms.<sup>(7)</sup> Phytoestrogens are natural substances from plants of differing

chemical structure than estrogens, but having very similar actions, so that they are called estrogen-like substances and are also known as herbal estrogens. These compounds can bind to estrogen receptors (ER- $\alpha$  and ER- $\beta$ ) and possess estrogenic activity, but are also weakly anti-estrogenic.<sup>(8)</sup> The various types of phytoestrogens occurring in plants have two important effects on humans, i.e. estrogenic and anti-estrogenic, depending on endogenous estrogen and estrogen receptor concentrations, so that these phytoestrogens are also known as selective estrogen receptor modulators (SERM), having both agonistic and antagonistic effects.<sup>(9)</sup>

Isoflavones are phytoestrogens abundantly found in soy beans, and several studies have demonstrated that isoflavones are the best among the phytoestrogens. Soy beans are consumed in considerable quantities in Indonesian communities and other Asia populations. The prevalence of chronic and degenerative diseases were significantly lower in Asian populations with a high consumption of foods rich in soy beans, in comparison with American or European populations.<sup>(10-12)</sup>

The results of a systematic review in the Cochrane Collaboration did not yield conclusive facts or evidence on the benefits of phytoestrogens on vasomotor symptoms. In spite of this, several of the most recent studies reported that phytoestrogens (particularly soy isoflavone extract) can significantly relieve hot flushes, improve plasma lipid profile, and inhibit the development of atherosclerosis, thus decreasing the risk of cardiovascular disease.<sup>(13,14)</sup> The aim of the present study was to evaluate the effect of soy isoflavone supplementation on menopausal symptoms in healthy postmenopausal women in Indonesia.

## METHODS

### Design of the study

This study was a community-based double blind randomized controlled trial conducted in South Jakarta from January to April 2010.

### Study subjects

The inclusion and exclusion criteria for recruitment of the postmenopausal women aged 48-60 years for this study, have been reported previously.<sup>(15)</sup>

### Sample size

This study was part of a larger investigation examining the effects of soy isoflavone supplementation on specific immune responses in postmenopausal women. Sample size determination and sampling techniques have been reported previously.<sup>(15)</sup>

### Intervention

Subjects were randomly assigned to two groups, the isoflavone group receiving 250 mg of 40% soybean isoflavones (equivalent to 100 mg soy isoflavone) + 500 mg calcium carbonate, and the control group receiving 500 mg calcium carbonate only. The intervention was administered continuously for 12 weeks at a dosage of 1 x 1 tablet daily. The supplement tablets were prepared by PT Ikapharmindo Putramas pharmaceutical company on special license of the Board for Supervision of Drugs and Foods of the Republic of Indonesia (*Badan Pengawasan Obat dan Makanan Republik Indonesia*, BPOM-RI).

### Assessment of menopausal symptoms

The subjects were asked to fill in the menopause rating scale (MRS) questionnaire to assess their menopausal symptoms. The MRS questionnaire used in this study is an official Indonesian translation following the International Methodological Recommendations for the Linguistic & Cultural Adaptation of HRQOL measures, and has been validated in Indonesia in a trial involving 1000 respondents. The menopausal symptoms evaluated by the MRS instrument comprise 3 dimensions, viz. psychological (score  $\geq 2$ ), somato-vegetative/vasomotor (score  $\geq 3$ ) and sexual/urogenital (score  $\geq 1$ ). Furthermore, using the established criteria, the subjects are categorized into a group

without or a few symptoms (score 0–4) and one with symptoms (score  $\geq 5$ ). The results of a reliability test on MRS yielded a total score  $\alpha=0.84$  (internal consistency coefficient) and a test-retest correlation coefficient of 0.8.<sup>(16,17)</sup>

### Assessment of dietary intake

Recording and calculation of dietary intake (carbohydrate, fat, protein and isoflavones) was done by a trained nutritional enumerator using the 24-hour food recall method. The dietary intake was also assessed using the Food Record method on 3 days of the week, namely 2 work days and 1 holiday (Saturday or Sunday). Assessment of the quality and quantity of dietary isoflavone intake was based on the completeness of soy isoflavone-containing foods and the weekly frequency of consumption using the Semi-Quantitative Food Frequency Questionnaire (SQ-FFQ), which comprises a list of soy isoflavone-containing foods. The subjects were divided into quintiles, viz. i)  $Q_1$  low isoflavone intake in foods, and ii)  $Q_2 - Q_5$  adequate isoflavone intake in foods.

### Anthropometric measurements

To assess nutritional status, the body mass index (BMI) was calculated using the formula  $BMI = \text{weight in kilograms divided by height in square meters}$ . Height was measured to the nearest 0.1 cm using a portable microtoise, while weight was measured to the nearest 0.1 kg using portable Sage scales. The criteria for BMI were according to the guidelines of the World Health Organization (WHO), namely normal (18.5-25.0  $\text{kg/m}^2$ ), mildly overweight (25.1-27.0  $\text{kg/m}^2$ ) and severely overweight ( $>27 \text{ kg/m}^2$ ).<sup>(18)</sup>

### Ethical clearance

This study was approved by the Research Ethics Committee, Faculty of Public Health, University of Indonesia.

### Data analysis

Data processing and analysis for this study was performed using the software Statistical

Table 1. Distribution of menopausal symptoms at baseline by treatment group

	Treatment group		p
	Isoflavone (n=27)	Control (n=29)	
Total MRS score	7.4 (6.6)	7.4 (6.3)	0.996*
Menopausal symptoms:			
Present (score $\geq 3$ )	59.3	51.7	0.602**
Absent (score 0-4)	40.7	48.3	
Psychological			
Present (score $\geq 2$ )	55.6	51.7	0.774**
Absent (score 0-1)	44.4	48.3	
Somatic/vasomotor			
Present (score $> 3$ )	59.3	51.7	0.571**
Absent (score 0-2)	40.7	48.3	
Sexual/urogenital			
Present (score $> 1$ )	48.1	51.7	0.789**
Absent (score 0)	51.9	48.3	

Mean (standard deviation), \*independent t-test, values are expressed as percentage of subjects, \*\*Chi-square test  
MRS = menopause rating scale

Package for Social Sciences (SPSS) version 17. Data were tested for normality of distribution using the Kolmogorov-Smirnov test of normality. A comparability test was performed between subject characteristics in the isoflavone and control group. The chi-square test or Fisher exact test was performed to determine the presence or absence of statistically significant differences (significance level  $p < 0.05$ ) in the number of subjects with menopausal symptoms before and after supplementation in the isoflavone group and the control group.

## RESULTS

### MRS scores at baseline

Table 1 below lists the total MRS score, number of subjects with menopausal symptoms and the three symptom dimensions (psychological, somatic/vasomotor and sexual/urogenital). At baseline mean total MRS score in the isoflavone group was  $7.4 \pm 6.6$  and in the control group  $7.4 \pm 6.3$ , thus not being significantly different ( $p = 0.996$ ). There were also no statistically significant differences in the three symptom dimensions between both treatment groups.

### Effect of isoflavones on menopausal symptoms

In Table 2 below, it is apparent that after daily supplementation of 100 mg soy isoflavones for 12 weeks, in spite of the greater number of subjects with menopausal symptoms in the isoflavone group, there were no statistically significant differences between the isoflavone group and the control group. There were also no statistically significant differences in the number of subjects with psychological, vasomotor, and urogenital symptoms between the isoflavone group and the control group, although there were more subjects in the isoflavone group with symptoms in the three dimensions. This indicates that supplementation of 100 mg soy isoflavones for 12 weeks was unable to relieve the menopausal symptoms suffered by the postmenopausal women.

Table 3 below shows that in the overall analysis of subjects, the number of subjects with menopausal symptoms after supplementation decreased both in the isoflavone group and control group, but the decrease was lower in the isoflavone group in comparison with the control group ( $p = 0.103$ ). In subgroup analysis, the overall number of subjects with menopausal

Table 2. Menopausal symptoms and the three symptom dimensions in postmenopausal women after supplementation, by treatment group

Dependent variable	Treatment group		p *
	Isoflavone (n = 27)	Control (n = 29)	
Menopausal symptoms(+)	40.7	20.7	0.103
Psychological symptoms(+)	48.1	37.9	0.440
Vasomotor symptoms (+)	22.2	13.8	0.411
Urogenital symptoms (+)	40.7	34.5	0.629

Values are expressed as percentage of subjects \*Chi-square test

symptoms also decreased after supplementation, both in the isoflavone group and the control group. Regarding the subjects with menopausal symptoms who also had adequate dietary isoflavone intake, the number decreased slightly more in the isoflavone group (31.8%) than in the control group (27.3%) ( $p=0.322$ ).

In the subgroup with psychological symptoms, for all subjects after supplementation there was a decrease in their numbers in the isoflavone group as well as the control group, without a statistically significant difference between the two groups ( $p=0.440$ ). There was in general also a decrease in psychological symptoms after supplementation in the isoflavone and control groups, except in subjects with inadequate dietary isoflavone intake (40%) ( $p=0.222$ ).

Similarly, in all subjects with somatic or vasomotor symptoms, there was after supplementation no statistically significant decrease in their numbers, both in the isoflavone and the control group ( $p=0.411$ ). In the subgroup analysis, the isoflavone group had no significantly larger decreases in the number of subjects with vasomotor symptoms and above normal baseline BMI or inadequate dietary isoflavone intake in comparison with the control group. However, subjects with normal baseline BMI and those with adequate dietary isoflavone intake, had a larger decrease of respectively 45.4% and 45.5% in number of subjects with vasomotor symptoms in the isoflavone group than in the control group, although there was no statistically

significant difference between the two groups ( $p=1.000$ ). This demonstrates a tendency for isoflavone supplementation at a dosage of 100 mg for 12 weeks to decrease vasomotor symptoms in postmenopausal women of both of above subgroups. It cannot be ascertained why precisely in subjects with inadequate isoflavone intake, the decrease in the number of subjects with menopausal symptoms was greater in the control group (57.1%) than in the isoflavone group ( $p\geq 0.05$ ).

In Table 3 below it may also be seen that in the analysis of all subjects with urogenital symptoms, the differences in decreased number of subjects in the isoflavone and control groups were statistically not significant ( $p=0.629$ ). In the subgroup analysis, there was an 18.2% decrease in subjects with urogenital symptoms after receiving isoflavone supplements, this being twice the decrease in the control group ( $p=0.531$ ).

## DISCUSSION

This study shows that administration of soy isoflavone supplementation at a dosage of 100 mg per day for 12 weeks to postmenopausal women tended to decrease the incidence of menopausal symptoms, in comparison with the control group, but the results were statistically not significant. In the subgroup analysis there was a tendency for the administration of supplementation to decrease the incidence of menopausal symptoms in several subgroups.

Table 3. Percentages of relative differences (̂) in menopausal symptoms, and psychological, vasomotor, and urogenital symptom dimensions, before and after supplementation, by treatment group in all subjects and subgroups of postmenopausal women

	Menopausal symp bms treatment group		p *	Psychological symp bms treatment group		p *	Vasomotor symp bms treatment group		p *	Urogenital symp bms treatment group		p *
	Isoflavone (n=27)	Control (n=29)		Isoflavone (n=27)	Control (n=29)		Isoflavone (n=27)	Control (n=29)		Isoflavone (n=27)	Control (n=29)	
All subjects	-18.6	-31.0	0.1108	-7.5	-13.8	0.440	-37.1	-37.9	0.411	-7.4	-17.2	0.629
Baseline BMI												
BMI = Normal	-27.2	-33.3	0.591	-18.1	-22.2	0.374	-45.4	-33.3	1.000	-9.1	-22.2	1.000
BMI > Normal	-12.5	-30.0	0.121	0	-10.0	0.765	-31.3	-40.0	0.422	-6.2	-15.0	0.549
Daily dietary												
iso flavone intake	4.0	-4.7	0.222	4.0	-7.1	0.222	0	-7.1	0.040	4.0	-4.8	0.072
Inadequate	-31.8	-27.3	0.322	-18.1	0	1.000	-45.5	-31.8	1.000	-18.2	-9.1	0.531
Adequate												

\*Results of significance tests on the number of subjects with menopausal symptoms and with psychological, vasomotor, and urogenital symptoms, after supplementation between the isoflavone group and the control group, performed with chi square test or Fisher's exact test.

Values are expressed as percentages of relative differences in the number of subjects with menopausal symptoms and with psychological, vasomotor, and urogenital symptoms (+) before and after supplementation, computed according to the formula: percentage of subjects with symptoms (+) after supplementation minus percentage of subjects with symptoms (+) before supplementation]

BMI : body mass index

These subgroups comprised the subjects in the early postmenopausal group (urogenital symptoms), in those subjects receiving adequate daily dietary isoflavone intakes (psychological, urogenital, and vasomotor symptoms) and in those having a normal body mass index (BMI) (vasomotor symptoms), although there were no statistically significant differences between the isoflavone group and the control group. Essentially similar results were obtained in the Soy Estrogen Alternative study, which involved women aged 45–55 years experiencing one vasomotor symptom in 24 hours. This study found that the decrease in vasomotor symptoms was not due to isoflavones.<sup>(19)</sup>

In contrast, differing results were obtained in a placebo-controlled trial involving 80 postmenopausal women, where the menopausal symptoms were assessed by the Kupperman index. Significant improvement in menopausal symptoms was found with a daily supplementation of 100 mg isoflavones (70% genistein, 19% daidzein, and 11% glycitein) for 4 months, in comparison with a placebo. However, the daily frequency of hot flashes decreased only from  $11.3 \pm 0.3$  to  $8.2 \pm 0.5$  per day in the isoflavone group, while the reduction in hot flash frequency in the control group was from  $10.4 \pm 0.4$  to  $9.9 \pm 0.4$  per day.<sup>(20)</sup> In another study it was found that soy isoflavones were able to affect hot flashes only in combination with polyunsaturated fatty acids.<sup>(21)</sup> Statistically significant results were found in a meta-analysis of 17 randomized clinical trials on isoflavone supplementation and hot flash frequency.<sup>(22)</sup> This was in contrast with an earlier meta-analysis of 17 randomized isoflavone trials which showed variable results for soy isoflavones in their effects on hot flashes.<sup>(23)</sup> A third meta-analysis of 11 studies found that beneficial effects were only found with isoflavone supplements having a markedly higher genistein content, and not with those rich in daidzein.<sup>(24)</sup>

In view of the currently inconclusive evidence regarding the effect of soy isoflavone supplementation on menopausal symptoms, it is worth while to speculate on the thus far unexplained mechanism of action of isoflavones in the reduction of vasomotor symptoms. One of the explanations may be that isoflavones act on estrogen receptors, which are able to bind compounds such as natural estrogens and other chemically similar isoflavones.<sup>(9,14)</sup>

A Cochrane systematic review and meta-analysis performed by Jacobs et al.<sup>(25)</sup> and Bolanos et al.<sup>(26)</sup> on a number of studies aiming to evaluate the effectiveness of isoflavones on vasomotor symptoms using various methodologies, did not come to a clear conclusion, although there were indications of beneficial effects of soy isoflavones on the frequency and severity of hot flashes. The many soy isoflavone studies are heterogenous with regard to intervention and outcome assessment. Many questions arise as to the optimal dosage and duration of supplementation required to achieve the intended clinical response. Some experts call into question the duration of soy isoflavone administration used in a number of studies, which is considered to be too short for yielding a clinical response.

Similarly to estrogens, isoflavones also undergo several biochemical processes in the body. The activity of isoflavones at the cellular level depends on target tissue, tissue receptor status, and endogenous estrogen level. In premenopausal women with high circulatory endogenous estrogen levels, isoflavones may act as estrogen antagonists. On the other hand, in postmenopausal women with lower endogenous estrogen levels, isoflavones may exert the opposite effect, acting as estrogen agonists. In the present study, no assessment was done on endogenous estrogen and isoflavone levels after supplementation, thus it was not possible to determine their relationship with menopausal symptoms. The high genistein, daidzein and

glycitein content in the soy isoflavone supplementation may presumably modify the effects. Genistein is considered to be the most potent among the three soy isoflavones (genistein, daidzein, and equol). The study conducted by Ferrari concludes that in ordinary living conditions, a high dosage of isoflavones (60 mg genistein in 80 mg isoflavones) given for 12 weeks, can be used to treat hot flashes in postmenopausal women, because it gives better effects in comparison with placebo at a high level of safety.<sup>(27)</sup>

One limitation of the present study was that the data collected using the MRS questionnaire as a diagnostic instrument for the presence of menopausal symptoms, were self-reported on the basis of presence or absence and severity of the subjects' menopausal symptoms, thus tending to induce bias. Other studies used differing scoring systems, i.e. the Kupperman vasomotor scale and the simple severity scale. These instruments are more detailed in assessing frequency and severity of menopausal symptoms.

## CONCLUSION

Supplementation of 100 mg soy isoflavones for 12 weeks in postmenopausal women tends to reduce menopausal symptoms. Further studies are indicated to examine any correlations of amount (dosage) and route of administration (consumption) of soy isoflavones with their effects on menopausal symptoms.

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