The Journal of Nutrition
Nutrition and Disease

Consumption of a Flaxseed-Rich Food Is Not More Effective Than a Placebo in Alleviating the Climacteric Symptoms of Postmenopausal Women[1,2]

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Abstract

Our objective in this work was to test the effects of daily intake of bread produced with partially defatted ground flaxseed on the climacteric symptoms and endometrial thickness of postmenopausal women. A double-blind, placebo-controlled, randomized clinical trial was performed with 38 women who had been postmenopausal for 1–10 y and consumed 2 slices of bread containing 25 g of flaxseed (46 mg lignans) or wheat bran (<1 mg lignans; control) every day for 12 consecutive weeks. The outcome variables were the daily number of hot flashes, the Kupperman Menopausal Index (KMI), and endometrial thickness. The plasma lipid profile (total cholesterol and HDL, LDL, and VLDL cholesterol fractions and triglycerides) and the hormones estradiol, follicle-stimulating hormone, thyroid-stimulating hormone, and free thyroxine also were measured. Food intake was evaluated by means of 2 24-h recalls, before and after the treatment. Twenty patients in the study group and 18 in the control group completed the study. The general characteristics did not differ between the 2 groups at the start of the study. Both had significant, but similar, reductions in hot flashes and KMI after 3 mo of treatment. Moreover, endometrial thickness was not affected in either group. Our findings clearly show that although flaxseed is safe, its consumption at this level (46 mg lignans/d) is no more effective than placebo for reducing hot flashes and KMI. J. Nutr. 140: 293–297, 2010.

Introduction

With the growth of the elderly population, many women live up to one-third of their lives beyond menopause. This represents a serious public health challenge regarding the search for new alternatives to prevent and postpone diseases that can interfere with the quality of life of this population (1,2). There is an increasing number of women with contraindications for hormonal therapy or with a preference for more natural treatments because they fear the side effects or repercussions of clinical trials within this field (3,4).

Some epidemiological studies have shown that symptoms such as hot flashes and sweating are less prevalent and of lower intensity in Asian countries (5,6). Moreover, cardiovascular diseases, osteoporosis, and breast, cervical, and endometrial cancers have lower incidence in Asian countries (7). Adlercreutz et al. (8) showed that the urinary excretion of phytoestrogens, such as isoflavones and lignans, was 10–100 times greater among women who consumed a traditional Japanese diet compared with a Western diet. Phytoestrogens are substances present in foods that are structurally similar to estrogens and can perform weak estrogenic or antiestrogenic actions, depending on the concentration of endogen estradiol and the specific organ involved. Among the main types of phytoestrogens are lignans, which are found in most plants but at high concentrations in flaxseed, and isoflavones, which are abundant in soybeans and their derivatives (2,9).

The main lignan present in flaxseed is secoisolariciresinol diglycoside (SDG),[6] which needs to be converted by the human intestinal microbiota into enterodiol and enterolactone, the biologically active forms (9). Studies on isoflavones and lignans consumed in different ways have shown inconclusive results regarding effects on menopause symptoms (10–15). Not all studies had placebo controls (16,17). Some did not control for phytoestrogen intake from other sources, which could have generated some interference (17–19). Others used methods to evaluate the outcome variables that had not been validated for that purpose (10,11,15,17,20).

[1] Supported by Fundação de Amparo à Pesquisa do Estado de São Paulo (grants 2003/06717-2 and 2007/07747-3).
[2] Author disclosures: R. L. Simbalista, A. V. Sauerbronn, J. M. Aldrighi, and J. A. G. Arêas, no conflicts of interest.
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[6] Abbreviations used: FSH, follicle-stimulating hormone; HDL-C, HDL cholesterol; KMI, Kupperman menopausal index; LDL-C, LDL cholesterol; SDG, secoisolariciresinol diglycoside (flaxseed lignan precursor); T4, thyroxine (thyroid hormone); TSH, thyroid-stimulating hormone; VLDL-C, VLDL cholesterol.

Manuscript received July 31, 2009. Initial review completed August 21, 2009. Revision accepted November 6, 2009.
First published online December 9, 2009; doi:10.3945/jn.109.113886.

Biological and in vitro studies with soy isoflavones have shown their estrogen stimulation effect on endometrial cells (21), thereby suggesting that these compounds may have agonist action in these cells. On the other hand, studies on animals have shown that soy has a proliferative effect on the endometrium and few have investigated its effects on postmenopausal women (6,7,22). The data about flaxseed effects on these same biological targets are scarce, with some reports on sex steroid hormone levels (23). More information about how it affects either endometrial thickness or menopausal symptoms is needed.

Thus, our main objective in this study was to test the effects of daily consumption of bread produced with partially defatted ground flaxseed that is rich in lignans on the climacteric symptoms and endometrial thickness of postmenopausal patients.

Materials and Methods

Variables. The main outcome variables, i.e. hot flashes and climacteric symptoms, were measured using a daily record of the number of hot flashes and the Kupperman Menopausal Index (KMI) at the beginning of the intervention and after 3 mo.

The number of hot flashes and occurrences of night sweating were recorded in a diary that was handed out at the beginning of the study and collected every month. The monthly means were compared, calculated as the sum of the total number of hot flashes per day, divided by the total number of days in the month.

To evaluate the menopausal symptoms, the KMI was used. This index has been used for the last 50 y as a measurement for evaluating the main discomforts associated with menopause. It is composed of 11 items (hot flashes, paresthesia, insomnia, nervousness, depression, vertigo, fatigue, arthralgia, palpitation, headache, and tinnitus) that are evaluated by means of Likert scales (0, absent; 1, mild; 2, moderate; 3, intense) depending on the intensity. Each score is multiplied by a defined factor according to the contribution of that symptom to the index. The scoring ranged from 0 to 51 (mild <20; moderate 20–30; intense >30). The clinical evaluations for the KMI were always conducted by the same researcher at the beginning and at the end of 3 mo.

Biochemical tests were carried out for plasma evaluation of the lipid profile [total cholesterol, HDL cholesterol (HDL-C), LDL cholesterol (LDL-C), VLDL cholesterol (VLDL-C), and triglycerides] and of the following hormones: estradiol, follicle-stimulating hormone (FSH), thyroid-stimulating hormone (TSH), and free thyroxine (T4). Blood samples were drawn into a heparin-wetted syringe and plasma was harvested after centrifugation at $1500 \times g$ for 15 min. Cholesterol was measured by plasma treatment with cholesterol esterase followed by cholesterol oxidase that generates hydrogen peroxide, which is determined by peroxidase action coupled with 4-aminoantipyrine. The antipirylquinone imine formed in this latter reaction was measured at 500 nm with proper calibration curve (cholesterol kit, Labtest). Triacylglycerol was determined in plasma by lipoprotein lipase action to hydrolyze triacylglycerols releasing glycerol, which then was treated by glycerol kinase followed by glycerol 3-phosphate oxidase that liberates hydrogen peroxide, which was determined as above (triacylglycerols kit, Labtest). HDL-C was measured subsequent to the precipitation of the apoB-containing lipoproteins with sodium phosphotungstate magnesium chloride (Labtest, catalog no. Cat 13). The supernatant fraction was assayed for total cholesterol using the enzymatic kit for total cholesterol. LDL-C and VLDL-C fractions were calculated as proposed by Friedewald et al. (24). Fluorimetric assays for plasma estradiol, free T4, TSH, and FSH were conducted using the automated system Autodelfia (Delfia, Wallac Oy). All these laboratory assays were carried out at the Clinical Hospital of the School of Medicine, University of São Paulo, by the Central Laboratory division (research protocol PR 289).

Endometrial thickness was always evaluated by the same observer by means of the suprapubic and transvaginal routes. Endometrial homogeneity and linearity were also evaluated. The measurements of endometrial thickness were made on its greatest dimension, using longitudinal sections through the uterus. At least 3 measurements were made. The ultrasound equipment used was Phillips model HDI 5000 SonoCT, with a 2–5 MHz multifrequency transducer and a 5–9 MHz multifrequency endovaginal transducer, and GE model Voluson 730, with a 2–5 MHz convex multifrequency transducer and a 4–8 MHz endovaginal transducer.

The patients' diet was evaluated by means of 4 24-h recalls: 2 before the treatment and 2 during the last week of intervention, on different days of the week. This information was analyzed using the Nutrition Support software (Nutwin, version 1.5.2.51, 2005) of the Federal University of São Paulo, Brazil. The patients selected were instructed to avoid consuming flaxseed and soybeans and their derivatives during the intervention period and were provided with a list of the main foods that contain these components. Urine enterolactone and enterodiol excretions were not measured. However, the product formulation was such that the amount of added partially defatted ground flaxseed was high enough to reach a clear difference between the treatment groups.

Population. The women who participated in this study were recruited from among the patients seen at the Climacteric House of the Zerbini Foundation and the "Geraldo de Paula Souza" Teaching Health Center of the School of Public Health, University of São Paulo, between April 2005 and July 2006. The inclusion criteria were amenorrhea for at least 1 y, estradiol <73.4 pmol/L, FSH >39 IU/L, moderate to severe KMI (20–51), and at least 2 hot flashes/d. The exclusion criteria were the use of hormonal therapy during the last 3 mo, use of antibiotics during the previous month, use of antidepressives, use of phytoestrogen-base supplements, uncontrolled hypertension, thyroid disorder, diabetes mellitus, and allergies to any ingredient of bread.

All the patients selected signed the Informed Consent Form approved by the Research Ethics Committee of the School of Public Health, University of São Paulo, in accordance with the requirements of the CNS Resolution 196/96, under the research protocol no. 1019, 2003.

Product. Two types of bread were developed for the intervention. They were isocaloric, with similar lipid and fiber contents and similar appearance. The first contained partially defatted ground flaxseed and the second (control) had wheat bran and toasted barley for adjusting the fiber content and coloring. A single batch of partially defatted ground flaxseed was supplied by the company Pazze Ltda. and was stored under refrigeration (<8°C) during the whole period of the study. To maximize the lignan content (present in the fibrous portion of the seed) in the case bread and to adjust the lipid content in the bread, partially defatted flaxseed flour was used (reduction of 44% in the lipid content). Each daily portion provided the equivalent of 25 g of the whole seed and 46 mg of SDG, the precursor of mammalian lignans. The SDG content of the control bread was negligible. The formulation and macronutrient content of the intervention products are presented in **Table 1**.

The products were very similar in flavor and appearance and could not be differentiated by trained tasters. Nevertheless, opaque golden packaging was used. The content for fibers and lipid was very similar in the 2 products.

All production was carried out, fortnightly, in the industrial bakery of the Institute for Bread and Confectionary Development (São Paulo).

Intervention and randomization. A double-blind, placebo-controlled, randomized study was conducted over a 3-mo period. The patients selected underwent a gynecological consultation to assess their general health conditions, history of diseases, and the KMI. At the same time, they were weighed and height was measured for calculation of their BMI (kg/m^2). Their food intakes were assessed and blood pressures measured. One week before starting the study, the patients received a diary in which to note the number of hot flashes experienced (baseline) and whether they consumed 2 slices of bread every day. After this initial evaluation, the patients underwent blood tests and an ultrasound scan. The randomization of the patients was carried out by an employee of the Nutrition Department of the University of São Paulo using a computer-generated list. The same employee received the boxes containing the bread inside the opaque packages and was responsible for distributing

TABLE 1 Formulation and macronutrient content of bread made of flaxseed defatted flour and control bread

Ingredient, *g*	Flaxseed bread	Control bread
Flour (wheat + flaxseed; 70:30)	100	0
Mix (wheat + grits + barley; 84:14:2)	0	100
Sugar (sucrose)	5.5	4.0
Salt (NaCl)	2	2
Oil (canola oil)	5	10
Additives	1	1
Dried yeast	2	2
Water	80	58
Wheat gluten (80% pure)	8	0
Nutrient, *unit/100 g bread*		
Energy, *kJ*	879	963
Proteins, *g*	15.4	8.6
Lipids, *g*	1.40	1.60
Carbohydrates, *g*	33.2	44
Ash, *g*	1.50	1.75
Water, *g*	37.3	33.2
Fiber, *g*	11.2	10.9

the products in accordance with the randomization. Thus, the patients, physicians, and principal investigator were unaware of group assignments until the last patient had undergone her final examination. Each patient received the bread every 15 d, which was individually packed (2 slices in each pack), and was instructed to keep it frozen until the day of consumption, at whatever time and way, as a part of their habitual diet. The patients were instructed to note only the number of hot flashes, not the intensity or duration, in a diary covering the whole period and whether they consumed the 2 slices of bread every day. At the time of each bread delivery, the patients were questioned about side effects and about their consumption of foods that were rich in isoflavones and lignans. The adherence to bread consumption was investigated through the diaries. The maintenance of their regular diet was assessed by 4 24-h recalls, 2 at the beginning and 2 at the end of the intervention. At the end of the 12-wk period, the patients returned to the Climacteric House to repeat all of the initial examinations and evaluations. To investigate the acceptability and lack of capacity to identify which bread was consumed, the patients were asked whether they intended to continue consuming the product and which bread they believed they had consumed.

Statistical analysis. The descriptive analysis of the quantitative variables showed that they all presented normal distribution, with the exception of estradiol and endometrial thickness (Kolmogorov-Smirnov test). The comparative analysis between the groups was carried out by the *t*-Student's *t* est. The Wilcoxon's test was used to compare each group before and after 3 mo. The significance level was set as 5%. The analyses were carried out using SPSS 12.0 software.

Results

By the end of the study, the number of patients selected was 38, of whom 20 were in the study group and 18 in the control group. Among the selected women, only one in the placebo group did not complete the study, because she dropped out during the first month for a personal reason. The side effects reported to the investigator during the intervention included greater intestinal flow, flatulence, and a feeling of greater satiety. These factors may be explained by the elevated dietary fiber content in both types of bread. The breads were well accepted, with a mean consumption of 94% in both groups. Two patients in the placebo group said that they became somewhat tired of consuming the breads every day, from the halfway point of the intervention onwards. Because the breads were very similar in appearance (brown color) and rich in fibers, by the end of the study, almost all the patients believed they were consuming the flaxseed bread, even those who were in the placebo group.

TABLE 2 General characteristics of the patients before the intervention[1]

	Group	
Weight, *kg*	Flaxseed	65.4 ± 10.3
	Control	63.9 ± 13.3
Height, *m*	Flaxseed	1.57 ± 0.07
	Control	1.56 ± 0.06
BMI, kg/m^2	Flaxseed	26.4 ± 3.6
	Control	26.1 ± 5.0
Time postmenopausal, *mo*	Flaxseed	45.3 ± 27.0
	Control	42.1 ± 33.0
Age, *y*	Flaxseed	52.0 ± 2.9
	Control	52.7 ± 4.2

[1] Values are means ± SD, *n* = 20 (flaxseed) or 18 (control). Groups did not differ.

Prior to the intervention, general characteristics (weight, height, age, and number of months in postmenopause) did not differ between the 2 treatment groups (**Table 2**).

The initial KMI did not differ between the groups ($P = 0.97$), in accordance with the inclusion criteria, nor did the frequency of hot flashes, which was 8.5/d for both groups, (Table 4, wk 0).

Plasma lipid concentrations differed among the groups before the study (Table 4, wk 0). The flaxseed group had higher concentrations of total-, LDL-, and VLDL-C fractions and lower concentrations of triglycerides and HDL-C than the control group. In both groups, the initial total cholesterol concentration was above the maximum recommended value (5.18 mmol/L), as was LDL-C concentration in the flaxseed group, which was >3.37 mmol/L (25).

All of the patients had plasma TSH and free T4 concentrations within the expected limits (26). This control is important, because disorders in the thyroid gland can interfere with vasomotor symptoms such as hot flashes. All of the patients had estradiol concentrations <73.4 pmol/L and those of FSH >39 IU/L characteristic of the postmenopausal phase.

Energy and macronutrient intakes did not change in either group or differ between the groups, before or after the treatment (**Table 3**). These data demonstrate that, during the treatment period, the patients adhered to the dietary instructions that they had been given.

Although the plasma lipid profile differed between the groups prior to the study, there were no changes in either group after the 3-mo (12 wk) intervention, except for a decrease in HDL-C in the control group (**Table 4**).

TABLE 3 Daily energy and macronutrient intakes of the patients before and after the intervention with flaxseed and control bread[1]

	Flaxseed		Control	
	wk 0	wk 12	wk 0	wk 12
Energy, *kJ*	5041 ± 831	5330 ± 577	5401 ± 670	5367 ± 606
Proteins, *g*	54.5 ± 9.7	60.4 ± 10.9	69.4 ± 9.7	72.9 ± 13.8
Lipids, *g*	40.3 ± 8.0	40.6 ± 6.9	41.5 ± 7.0	40.3 ± 8.6
Carbohydrates, *g*	162 ± 23	169 ± 17	168 ± 23	161 ± 20
Fiber, *g*	17.4 ± 3.8	17.4 ± 3.9	16.7 ± 4.0	16.8 ± 4.1

[1] Values are means ± SD, *n* = 20 (flaxseed) or 18 (control). Groups did not differ from one another at either time and there were no changes within either group.

TABLE 4 Plasma biochemistry and menopausal symptoms of the patients before and after the intervention with flaxseed and control bread[1]

	Flaxseed		Control	
	wk 0	wk 12	wk 0	wk 12
KMI	20.9 ± 7.9	12.6 ± 6.7*	21.0 ± 8.6	12.9 ± 5.7*
Hot flashes, *n/d*	8.5 ± 4.3	5.2 ± 3.9*	8.5 ± 5.0	4.0 ± 2.4*
Endometrial thickness, *mm*	2.41 ± 0.75	2.89 ± 0.78	3.02 ± 3.02	3.56 ± 2.78
Total cholesterol, *mmol/L*	6.03 ± 0.87**	5.96 ± 1.13	5.18 ± 0.93	5.15 ± 0.84
HDL-C, *mmol/L*	1.61 ± 0.31**	1.59 ± 0.24	1.86 ± 0.42	1.73 ± 0.41*
LDL-C, *mmol/L*	3.83 ± 0.89	3.68 ± 1.03	2.87 ± 0.93	2.90 ± 0.86
Triglycerides, *mmol/L*	1.49 ± 0.80**	1.68 ± 1.01	1.00 ± 0.54	1.12 ± 0.5019
Estradiol, *pmol/L*	52.1 ± 11.0	53.2 ± 12.0	55.7 ± 18.0	53.2 ± 9.5
FSH, *IU/L*	80.6 ± 21.8**	79.7 ± 17.5	90.1 ± 31.5	84.0 ± 30.0*
TSH, *mIU/L*	1.69 ± 0.56	1.61 ± 0.59	1.43 ± 0.77	1.63 ± 0.80
Free T, *pmol/L*	13.5 ± 2.1	13.4 ± 1.5	12.9 ± 1.4	13.3 ± 1.7

[1] Values are means ± SD, $n = 20$ (flaxseed) or 18 (control). *Different from wk 0, $P < 0.05$. **Different from control, $P < 0.05$.

We followed the evolution of the number of hot flashes per day in each month (**Fig. 1***B*). Two patients in the control group did not have their number of flashes evaluated, because 1 was illiterate and the other had problems filling in the diary. From mo 1 onwards, the number of hot flashes decreased in both groups and the KMI at the end of the study was less than at the beginning (Fig. 1*A*,*B*); the groups did not differ from one another at either time. The behavior of the 2 study groups, regarding the KMI and hot flashes, presented a similar trend (Fig. 1*A*,*B*). In both, the 2 groups did not differ at the beginning or at the end of the study.

Discussion

The 2 study groups responded similarly to the intervention (Fig. 1; Table 4).

The control group had significant reductions in plasma HDL-C and FSH concentrations after the intervention. Although some biological and clinical assays (27,28) on flaxseed have shown its capacity to reduce total- and LDL-C, this did not occur in the present intervention; these values did not vary during the study. Other clinical studies on hypercholesterolemic menopausal women (17,29) support these results as they did not find changes in concentrations of total cholesterol or lipoprotein fractions after the consumption of 40 g/d of flaxseed.

Both groups had significant reductions in climacteric symptoms (KMI) and occurrences of hot flashes. Randomized studies with placebo have shown that the placebo effect on hot flashes ranged from 20 to 30% in number and severity over the first 4 wk (30).

Menopausal symptoms are very frequent and have a negative impact on the quality of life of many women. Thus, many types of alternative treatments have been investigated, but none have demonstrated the same efficacy as sex steroids. Recent discussions about the use of hormonal therapy show that physicians and patients need to consider, at the time of deciding on the treatment, not only the relieving of vasomotor symptoms but also the risk of developing cardiovascular diseases, breast cancer, osteoporosis, and thromboembolism. Mom et al. (31) reported that the placebo effect on hot flashes during the first month of treatment affected ~25% of the patients, with an improvement in the symptoms of at least 50%. The improvement (reduction) in the number of hot flashes among women taking placebo has been observed in studies that also used diaries as a means of measuring the frequency and severity of these symptoms. These studies show the importance of double-blind, placebo-controlled trials for testing the efficacy of a treatment in relation to these symptoms.

There are few studies assessing the effects of phytoestrogens on climacteric symptoms among postmenopausal women (10–15). In this study, using a natural food rich in lignans and another food as the control, we did not find significant differences in symptoms between the 2 groups after 12 wk of

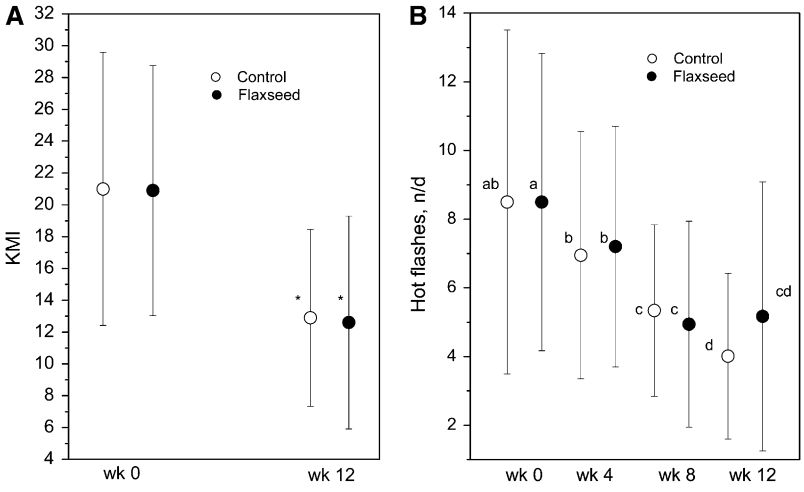

FIGURE 1 KMI (*A*) and daily hot flashes (*B*) in patients during the 12-wk intervention with flaxseed and control breads. Values are means and 95% CI, $n = 20$ (flaxseed) or 18 (control). (*A*) *Different from wk 0, $P < 0.05$; groups did not differ at either time. (*B*) Within a group, means without a common letter differ, $P < 0.05$. Groups did not differ at any time.

treatment. In both groups, the patients had a significant reduction in the number of hot flashes and in the KMI, in relation to the beginning of the treatment, but the groups did not differ at the end of the treatment. This improvement may be partly related to decreasing willingness to mark the symptoms correctly in the diary as time passed. However, all the patients who were involved in the study had good adherence throughout the intervention period, as confirmed by their assiduity at their fortnightly return visits.

Some studies that reported improvements in vasomotor symptoms evaluated, by means of a diary, not only the number of episodes of flashes but also the intensity of these symptoms (4). In the present trial, the intensity of the flashes was evaluated only at the beginning and end of the treatment through the KMI evaluations.

Although the breads supplied a high quantity of vegetable lignans (46 mg/d), it would be interesting to confirm, using urine tests, what increase there was in enterodiol and enterolactone excretions. For these metabolites to be excreted, the vegetable lignans need to be transformed into mammalian lignans by bacteria from the intestinal tract. Lewis et al. (4) supplied an equivalent amount (50 mg) of lignans in the form of muffins and observed a marked increase in the total quantity of these metabolites in urine.

Administration of 46 mg/d of lignans in the form of bread is no more effective than placebo for reducing hot flashes and the KMI. Endometrial thickness was not affected by either. We conclude that, in this trial, the phytoestrogens from flaxseed did not significantly affect menopausal symptoms, compared with placebo. However, this study confirms the importance of the placebo group for comparing the effects of other treatments on these symptoms.

Acknowledgments

We thank Dr. Sergio Kobayashi from the “Instituto de Radiologia da USP” (Radiology Institute, University of São Paulo) for his technical assistance in measuring endometrium thickness. R.L.S. and J.A.G.A. designed research and wrote the paper, V.S.A. and J.M.A. conducted research. All authors read and approved the submitted manuscript.

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