CLINICAL RESEARCH STUDY

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Side Effects of Phytoestrogens: A Meta-analysis of Randomized Trials

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ABSTRACT

BACKGROUND: Phytoestrogens are widely used by postmenopausal women for the treatment of the climacteric syndrome. The risk of adverse effects of this treatment, however, is unknown.

METHODS: Using a fixed-effects model, we performed a meta-analysis of side effects comparing phytoestrogen treatment with placebo or no treatment in randomized controlled trials.

RESULTS: We identified 174 randomized controlled trials. Side effects were reported in 92/174 randomized controlled trials with 9629 participants. The overall incidence of side effects in the phytoestrogen and control groups was 2019/5502 (36.7%) and 1824/4806 (38.0%), respectively ($P = .2$; incidence rate ratio [IRR] 1.01; 95% confidence interval [CI], 0.95-1.08). Comparing various side effect categories, we found significantly higher rates of gastrointestinal side effects among phytoestrogen users ($P = .003$; IRR 1.28; 95% CI, 1.08-1.50). Gynecological (IRR 0.94; 95% CI, 0.74-1.20), musculoskeletal (IRR 1.20; 95% CI, 0.94-1.53), neurological (IRR 0.91; 95% CI, 0.70-1.19), and unspecific side effects (IRR 0.95; 95% CI, 0.88-1.03) were not significantly different between groups. Within side effect categories, we found no significantly higher rates of side effects in women using phytoestrogens. Specifically, the rates of hormone-related side effects such as endometrial hyperplasia, endometrial cancer, and breast cancer were not significantly different between groups.

CONCLUSIONS: Based on the available evidence, phytoestrogen supplements have a safe side-effect profile with moderately elevated rates of gastrointestinal side effects. Rates of vaginal bleeding, endometrial hyperplasia, endometrial cancer, and breast cancer were not significantly increased among phytoestrogen users in the investigated studies.

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KEYWORDS: Climacteric syndrome; Hormone replacement; Meta-analysis; Phytoestrogens; Soy

Phytoestrogens are widely used by women for the treatment of climacteric syndrome complaints. Data from large-scale randomized trials and epidemiologic studies such as the Womens' Health Initiative and the One Million Women Study have challenged the safety of hormone replacement therapy and have led to an increased interest in phytoestrogens as an alternative treatment of the climacteric syndrome. Generally, phytoestrogens can be divided into 3 groups: flavonoids such as genistein, naringenin, and kaempferol; coumestans such as coumestrol; and lignans such as enterodiol and enterolactone. The best-studied phytoestrogenic compounds are isoflavones found in red clover and soy, for example, genistein, formononentin, biochanin A, and daidzein.[1]

It has been demonstrated that phytoestrogens are weak estrogen agonists acting via the estrogen receptor alpha and beta as well as through alternative signaling pathways in a receptor- and cell type-specific manner. The relative affinities of phytoestrogens to the estrogen receptor alpha as well as estrogen receptor beta are more than 1000-fold lower than that of estradiol.[2] Some phytoestrogens, for example, zearalenone, also exhibit estrogen antagonistic activity, but most phytoestrogens, including the flavonoids present in

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soy foods, only show agonistic activities. Therefore, systemic treatment with phytoestrogens can be expected to exert weak estrogen agonistic effects on various tissues. Whether or not treatment with phytoestrogens is associated with unwanted hormone-related side effects such as endometrial hyperplasia, endometrial cancer, and breast cancer, is unknown.

Based on these biologic properties of phytoestrogens, the safety of phytoestrogen supplementation has been challenged. Genistein, for example, antagonizes the inhibitory effect of tamoxifen on breast cancer cell growth in vivo and increases expression of estradiol-responsive genes.[3] Likewise, genistein negates the inhibitory effect of letrozole on the growth of aromatase-expressing human breast cancer cells.[4] Genistein and daidzein stimulate the formation of genotoxic metabolites of estradiol and inhibit the detoxification of catechol and quinone estrogens in estrogen-responsive tumor cells. Soy isoflavones decrease the catechol-O-methyltransferase-mediated inactivation of 4-hydroxyestradiol in human breast cancer cell lines such as MCF-7.[5] These experimental effects, however, are dose-dependent, and it is unclear whether these in vitro properties of phytoestrogens translate into an increased risk of hormone-related side effects such as endometrial cancer and breast cancer in women using phytoestrogens. To clarify the safety profile of phytoestrogens in this regard, we aimed to summarize the side effects and adverse events of phytoestrogen supplements reported in randomized controlled trials.

CLINICAL SIGNIFICANCE

- Phytoestrogen supplements have a safe side effect profile.
- In phytoestrogen supplement users, gastrointestinal side effects occur more often, compared with placebo or no treatment.
- Among phytoestrogen users in the investigated studies, there was no significant increase in rates of vaginal bleeding, endometrial hyperplasia, endometrial cancer, and breast cancer.

MATERIALS AND METHODS

Study Selection

We searched PubMed and the Cochrane controlled trials register (search terms: phytoestrogens, isoflavones, treatment, clinical trial, randomized) to identify randomized controlled trials, systematic reviews, and meta-analyses of randomized controlled trials assessing phytoestrogen teatment. Studies were included if they were published as original reports in English. Side effects and adverse events were summarized in each study. We included only studies assessing women. Studies assessing women and men were included, if the participating women were analyzed separately. Side effects were counted per side effect, that is, individual women could have more than one side effect. In cross-over studies, side effects were counted per side effect in all treatment groups. Multiple studies describing the same study population were included once. In this case, the original publication was used, that is, the one with the earliest date of publication.

Phytoestrogens were defined as substances with a defined amount of isoflavones, lignans, or coumestans. Two authors assessed eligibility of the studies and extracted data. Missing information and additional trials were not sought from authors.

We recorded the adequacy of treatment allocation concealment and considered trials to have adequate concealment if they described satisfactory procedures to conceal treatment allocation such as coded identical containers or centralized randomization. We also recorded blinding of participants and outcome assessors, use of intention-to-treat analysis, and the number of participants who withdrew or were lost to follow-up.

For each study and each type of side effects, we computed an incidence rate ratio (IRR) as follows: IRR = incidence rate in the phytoestrogen group/incidence rate in control group. The incidence rate was defined as the number of side effects reported divided by person-time. Because of the large proportion of studies reporting zero side effects of some type, we added 0.5 to the number of side effects and 1 to the number of patients in each group to yield finite incidence rate ratios. The variance of the logarithm of IRR (logIRR) was computed as:

$$1/\text{side effects in the phytoestrogen group} + 1/\text{side effects in control group}.$$

The standard error was calculated by the square root of the variance; 95% confidence intervals for individual IRRs were computed by exp (logIRR $\pm$ 1.96 standard errors). We used IRRs instead of odds ratios or relative risks because the number of reported side effects was potentially larger than the sample size, because the same participant may have reported several side effects. IRRs of individual studies were combined using a weighted mean of logIRR with weights given by the reciprocal variance of each study. A fixed-effects model was used for meta-analysis because no heterogeneity was detected ($P > .9$ in all analyses). Our analysis did not consider dependency of multiple side effects reported by the same patient because this information was not available. For specific side effects, we computed exact P-values by randomly distributing the recorded incidences of each study between groups, generating 100,000 permutations of the IRR under the null hypothesis of no group difference; and computing a P-value as the relative frequency of permuted IRRs as extreme as or more extreme than the

IRR observed in the original data. These exact *P*-values were then corrected for multiple testing by Benjamini and Hochberg's correction.[6]

The influence of clinical and epidemiologic variables such as patient age, region of study origin, phytoestrogen dosage, duration of phytoestrogen therapy, and mode of control group design (placebo vs. no treatment) on the occurrence of side effects was assessed using analysis of variance with the logIRR as dependent variable, weighting the studies by the reciprocal standard error. For all statistical analyses, we used the R package rmeta (R Foundation for Statistical Computing, Vienna, Austria, 2008).

RESULTS

We identified 174 randomized controlled trials comparing phytoestrogen treatment with placebo or no treatment in women. In 82/174 studies, no side effects or adverse events were reported. These studies were excluded from the analysis. Side effects were reported in 92 randomized controlled trials.[7-98] Median treatment duration in these trials was 6.2 months. Table 1 (available online) describes study details of the 92 randomized controlled trials included in the analysis. Overall, 9629 women were investigated, with 5502 and 4806 women in the phytoestrogen and control groups (including cross-over trials), respectively. The overall incidence of side effects in the phytoestrogen and control groups was 2019/5502 (36.7%) and 1824/4806 (38.0%), respectively ($P = .2$; IRR 1.01; 95% CI, 0.95-1.08). Figure 1 demonstrates a Forest plot of side effects in 92 studies comparing women taking phytoestrogens and controls. Table 2 lists side effects in the phytoestrogen and control groups broken down in various side effect categories: gynecological, gastrointestinal, musculoskeletal, neurological, and others. Specifically, we found that there was a statistically significant difference between the phytoestrogen and control groups regarding the frequency of gastrointestinal side effects ($P = .003$; IRR 1.28; 95% CI, 1.08-1.50), but not gynecological (IRR 0.94; 95% CI, 0.74-1.20), musculoskeletal (IRR 1.20; 95% CI, 0.94-1.53), neurological (IRR 0.91; 95% CI, 0.70-1.19), and unspecific side effects (IRR 0.95; 95% CI, 0.88-1.03). Figure 2 demonstrates a funnel plot indicating that there was no publication bias regarding the incidence of side effects. Figure 3 demonstrates a Forest plot of the IRRs of side effects according to different study characteristics such as patient age, region of study origin, phytoestrogen dosage, duration of phytoestrogen therapy, and mode of control group design (placebo vs no treatment), demonstrating that patient age and region of study origin, but not phytoestrogen dosage, duration of phytoestrogen therapy, and mode of control group design (placebo vs no treatment) affected the risk of side effects.

We separately evaluated the effect of study duration on the occurrence of side effects. When comparing the IRRs of side effects in studies with a study duration of <6 months vs. >6 months (IRR 1.14; 95% CI, 0.92-1.03 [54 studies] vs IRR 0.93; 95% CI, 1.00-1.09 [38 studies]; $P = .7$), <12 months vs >12 months (IRR 0.98; 95% CI, 1.08-1.19 [76 studies] vs IRR 0.88; 95% CI, 0.96.1.05 [16 studies]; $P = .04$), and <24 months vs ≥24 months (IRR 0.97; 95% CI, 1.04-1.12 [87 studies] vs IRR 0.74; 95% CI, 0.86-1.01 [5 studies]; $P = .01$), we found that women using phytoestrogens for a longer period of time reported fewer side effects than women enrolled in studies with a shorter study duration.

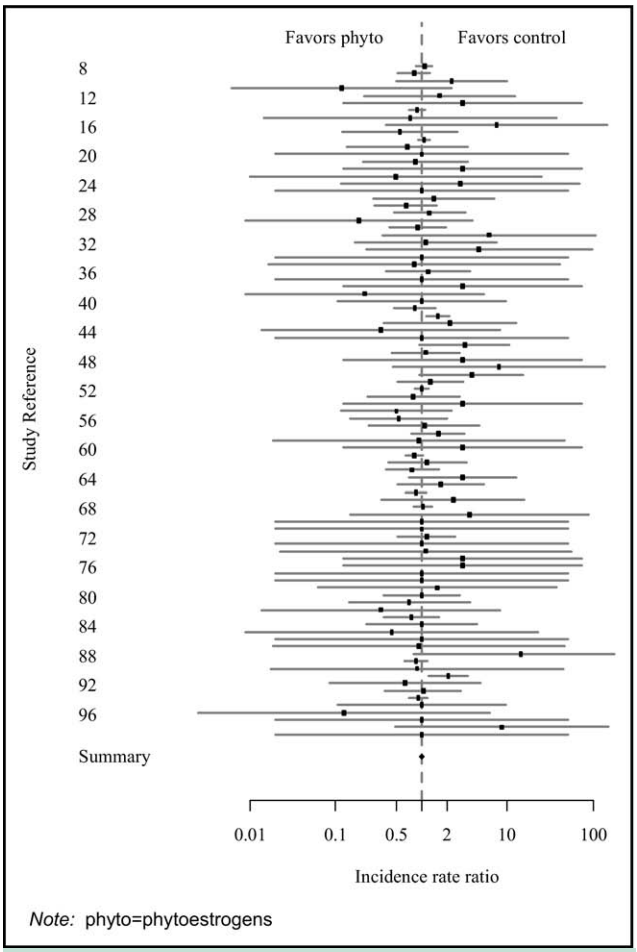

Figure 1 Forest plot showing incidence ratios and 95% confidence intervals of side effects in 92 randomized trials comparing phytoestrogens and placebo/no treatment. Phyto = phytoestrogens.

Tables 3 and 4 describe gynecological and gastrointestinal side effects in detail. Within these side effect categories, we found no significantly higher rates of side effects in women taking phytoestrogens compared with controls. Specifically, the rates of hormone-related side effects such as endometrial hyperplasia (13 vs 6 cases; $P = .6$) and breast cancer (11 vs 5 cases; $P = .9$) were not significantly different between women taking phytoestrogens and controls. One case of endometrial cancer was recorded in the investigated studies diagnosed 2.8 months after study entry.[65] Newly diagnosed breast cancer cases were observed 4.7, 6, 12, 15, and 24 months after study

Table 2 Categories of Adverse Events or Side Effects

	Gynecological or Urinary AEs or SEs (%)	Gastrointestinal AEs or SEs (%)	Musculoskeletal AEs or SEs (%)	Neurological or Sensory AEs or SEs (%)	Nonspecific or Other AEs or SEs (%)	Undefined AEs or SEs (%)
Phytoestrogens (n = 5502)	153 (7.8)	353 (17.9)	156 (7.9)	121 (6.1)	377 (19.1)	813 (41.2)
Controls (n = 4806)	117 (6.6)	239 (13.4)	112 (6.3)	101 (5.7)	379 (21.3)	832 (46.7)
IRR* (95% CI)	0.94 (0.74-1.20)	1.28 (1.08-1.50)	1.20 (0.94-1.53)	0.91 (0.70-1.19)	0.95 (0.88-1.03)	0.93 (0.77-1.14)
P-value	0.612	0.003	0.143	0.481	0.189	0.451

AEs = adverse events; SEs = side effects; *IRR = incidence rate ratio.
Percentages in parentheses are given per row.

entry. Both low- and high-dose preparations were used, and there was no pattern regarding a diagnosis of breast cancer preferentially in women after a longer duration of phytoestrogen use.

As to the qualitative analysis of the investigated studies, we found that 82/92 studies had adequate concealment of treatment allocation[7-22,24-26,28-36,38-43,45-52,54-58,61-79,81-94,97-98] and 21/92 studies had centralized randomization.[7-17,19,21-22,24-35,37-58,60-98] Blinding of participants and outcome assessors was performed in 81/92 trials,[7-22,24-42,44-57,61-72,74,77-94,98] whereas blinding of participants but not outcome assessors, was performed in 11/92 trials.[23,43,58-60,73,75-76,95-97] In 58/92 studies, >10% of study participants withdrew or were lost to follow-up.[8,10-19,22-23,26-30,33,38-42,45,47-58,60-61,65,67-70,72,75,78-82,84-85,87-90,92,98] Intention-to-treat analysis was reported in 21/92 studies.[13,18,19,27-29,41-43,45,49,51-52,54,57,67,77,89,91,93,98]

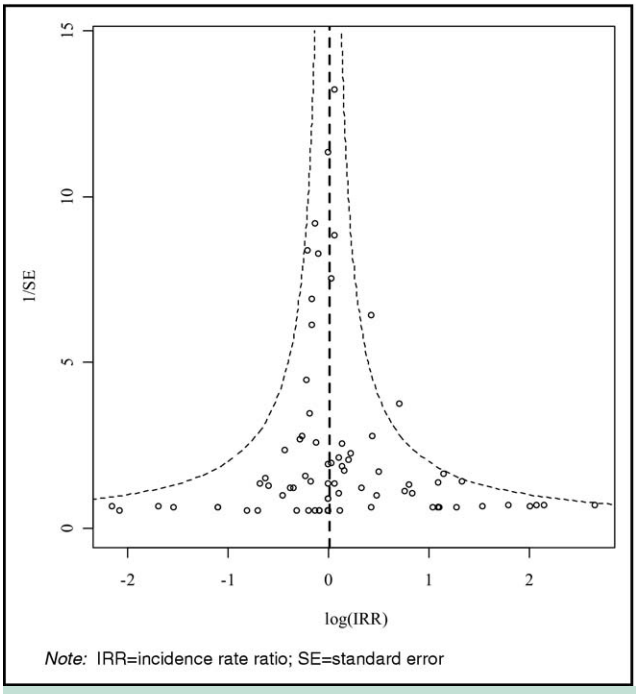

Figure 2 Funnel plot showing logarithmized incidence ratios of side effects. IRR = incidence rate ratio; SE = standard error.

Dropout rates were reported in 90/92 studies.[7-61,63-95,97,98] The number of dropouts in the phytoestrogen and control groups was not statistically significantly different (646/5454 vs 525/4758, respectively [$P = .2$]). Side effects of the study medication, however, were cited significantly more often as reason for dropout by women using phytoestrogens, compared with controls (199/5454 and 125/4758 of patients, respectively [$P = .004$]).

In individual studies, a statistically significant difference in the incidence of side effects between the phytoestrogen and control groups was reported in 2/92 randomized controlled trials.[7,87] Specifically, Albertazzi et al. reported significantly higher rates of bloatedness (7 vs 0 cases) and back pain (10 vs 2 cases) in a 12-week cross-over study of 100 postmenopausal women comparing 90 mg of genistein per day with placebo.[7] One long-term study over 5 years examined 298 women and reported a higher rate of endometrial hyperplasia without atypia in women taking 150 mg of isoflavone tablets per day compared with placebo (6 vs 0 cases, respectively). Specifically, all 5 cases of simple hyperplasia and 1 case of complex hyperplasia occurred after 5 years of treatment. No cases of endometrial hyperplasia with atypia or endometrial carcinoma were observed in this study.[87]

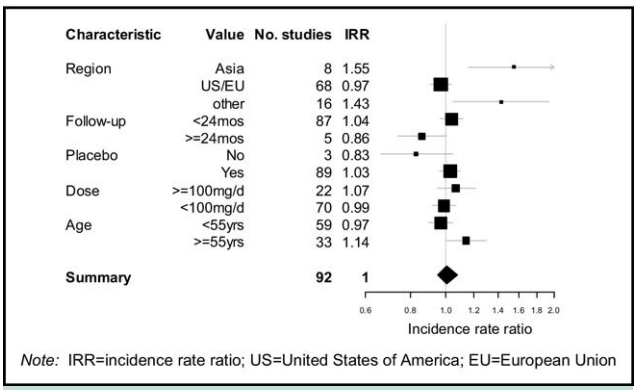

Figure 3 Forest plot of incidence ratios of side effects according to different study characteristics. IRR = incidence rate ratio; US = United States of America; EU = European Union.

Table 3 Gynecological and Urinary Adverse Events or Side Effects

	Vaginal Bleeding	Vaginal Spotting	Nipple Discharge	Breast Pain, Enlargement or Mastodynia	Breast Cancer (Breast Cancer Recurrence)	Endometrial Hyperplasia	Pelvic Discomfort	Nycturia	Others or Undefined
Phytoestrogens (n = 5502)	48	5	0	12	11 (2)	14	1	1	48
Controls (n = 4806)	29	1	0	5	5 (0)	6	0	0	48
P-value	0.9	0.4	—	1.0	0.9 (0.9)	0.6	1.0	1.0	1.0

DISCUSSION

Phytoestrogens are widely used by peri- and postmenopausal women for the treatment of the signs and symptoms of the climacteric syndrome. The risk of adverse effects of this treatment, however, is unknown. Specifically, a potential risk of hormone-related side effects such as endometrial and breast cancer is of concern because phytoestrogens have been demonstrated to act as weak estrogen agonists. Therefore, in the present study, we identified and analyzed 92 randomized controlled trials with 9629 participants regarding the occurrence of side effects of phytoestrogen treatment compared with placebo. We found that, based on the available evidence, phytoestrogen supplements have a safe side-effect profile with moderately elevated rates of gastrointestinal side effects such as abdominal pain, as well as myalgia and sleepiness. Phytoestrogen supplementation is not associated with an increased risk of breast or endometrial cancer.

We observed that the incidence rate ratio of side effects is affected by the region of study origin and patient age. Compared with studies from the US and Europe, studies conducted in Asia were more likely to record higher side effect rates in phytroestrogen-treated women than in controls. Also, phytoestrogen-treated women aged >55 years had higher rates of side effects compared with women aged <55 years. Because gastrointestinal side effects were the most prominent side effect category, these observations suggest that gastrointestinal tolerance of phytoestrogen supplements is reduced in older women and in Asian women whose diet is characterized by a high underlying consumption of phytoestrogens.

We also investigated whether the duration of phytoestrogen supplementation affected the risk of side effects. When using various study duration cut points such as 6, 12, and 24 months, we did not observe an association between study duration and a higher rate of side effects. To the contrary, side effects were observed less often in women using phytoestrogens for a longer period of time. These observations are somewhat reassuring, indicating that there are no cumulative dose effects of phytoestrogens over time.

Our study has strengths and weaknesses. For example, the method of meta-analysis reduces the likelihood of chance findings and inter-study variation based on ethnicity or treatment differences. Also, the large number of studies and study participants allows for the identification of side effects with small effect sizes and time-dependent trends towards changing rates of side effects with increasing study duration. On the other hand, we pooled the data of various phytoestrogen compounds, thus potentially masking the existence of different phytoestrogen-specific side effect profiles. Also, the median study duration of the investigated studies was 6.2 months, reflecting the fact that most of the published randomized controlled trials were of limited duration. Thus, we cannot rule out that rare side effects may occur in women on long-term treatment with phytoestrogens. This has to be acknowledged when interpreting the results of this study. Based on the available data, however, the use of phytoestrogens over a period of 2 years can be recommended.

In individual studies, a statistically significant difference in the incidence of side effects between the phytoestrogen and control groups was reported in 2/92 randomized controlled trials. One study reported a higher rate of endometrial hyperplasia without atypia after 5 years of phytoestrogen supplementation. This finding was never confirmed in another study. Thus, it cannot be ruled out that long-term

Table 4 Gastrointestinal Adverse Events or Side Effects

	Constipation	Diarrhea	Gastroenteritis	Bloating or Flatulence	Nausea or Vomiting	Abdominal Pain	Dyspepsia	Epigastric Pain	Others or Undefined
Phytoestrogens (n = 5502)	69	7	7	55	35	27	12	7	141
Controls (n = 4806)	57	6	2	36	22	9	4	0	107
P value	0.9	1.0	0.4	0.6	0.2	0.2	0.3	0.2	0.9

treatment may be associated with an increased risk of endometrial hyperplasia without atypia. However, there was no increased risk of endometrial or breast cancer in any individual study, as well as the meta-analysis of all studies.

Our findings have implications for women seeking safe treatment alternatives to hormone replacement therapy. Based on our findings, they can be assured that there is no indication of serious unwanted side effects of phytoestrogen treatment such as those found in women on hormone replacement therpy, for example, thrombosis, myocardial infarction, stroke, and breast cancer. It has to be acknowledged, however, that our study does not make any statement about the efficacy of phytoestrogen treatment, which has been discussed controversially.[99]

In summary, we found that phytoestrogen supplements have a safe side-effect profile with moderately elevated rates of gastrointestinal side effects, abdominal pain, myalgia, and sleepiness. Use of phytoestrogens is not associated with an increased risk of endometrial cancer or breast cancer.

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Table 1 Characteristics of Studies and Participants

First Author (Year of Publication)	Participants (Withdrawn)	Inclusion Criteria	Participant Characteristics	Study Duration	Study Medication
Albertazzi (2005)[7]	100 (1)	Amenorrhea ≥12 mos and ≤10 years; HRT ex ≥1 year; No secondary causes of bone loss	MA 53.5 years; MBMI 27	6 wks	Capsules (90 mg/d genistein)
Albertazzi (1998)[8]	104 (25)	Amenorrhea ≥6 mos or Oophorectomy ≥6 wks; ≥7 HF/d; FSH >50 IU/L; E2 <35 pg/mL HRT ex ≥6 wks	MA 52.9 years; MBMI 25.9	12 wks	Soy protein (76 mg/d isoflavones)
Allen (2007)[9]	216 (25)	Amenorrhea ≥12 mos or FSH >30 IU/L and LDL 3.37-4.92 nmol/L or Triglycerides >1.7 nmo/L;	MA 56.8 years; MBMI 27.94	12 wks	Soy protein (160 mg/d isoflavones)
Arjmandi (2005)[10]	87 (25)	Postmenopausal; Age <65 years; No HRT;	MA 54.5 years; MBMI 27.95	12 mos	Soy protein (60 mg/d isoflavones)
Arjmandi (2003)[11]	71 (29)	Postmenopausal	MA 62.1 years; MBMI 32.2	3 mos	Soy protein (88.4 mg/d isoflavones)
Atkinson (2004)[12]	205 (28)	Age 49-65 years; Breast density	MA 55.2 years; MBMI 25.3	12 mos	Promensil® (Red Clover; 43.5 mg/d isoflavones)
Atteritano (2007)[13]	389 (85)	Age 49-67 years; Amenorrhea ≥12 mos; Good general health; FSH >50 IU/L; E2 <100 pmol/L; BMD at femoral neck <0.795g/cm^2	MA 54.5 years MBMI 25	24 mos	Tablets (54 mg/d genisteinisoflavone)
Aubertin-Leheudre (2007)[14]	24 (6)	Age 50-70 years; Amenorrhea ≥12 mos; BMI >28; Waist circumference >88 cm; HRT ex ≥12 mos; Weight stable for 2 mos; Non-smoker; No medication that could influence glucose or lipid metabolism	MA 58 years MBMI 29.5	6 mos	Soy capsules (70 mg/d isoflavones)
Balk (2002)[15]	27 (8)	Age >40 years and Amenorrhea ≥12 mos or Age >30 years and Oophorectomy/ovarian failure; Intact uterus; Omnivorous	MA 57.4 years MBMI -	6 mos	Soy flour (100 mg/d isoflavones)

Table 1 Continued

First Author (Year of Publication)	Participants (Withdrawn)	Inclusion Criteria	Participant Characteristics	Study Duration	Study Medication
Blum (2003)[16]	30 (6)	Postmenopausal; Hypercholesterolemia; HRT ex ≥2 mos; LDL>130 mg/dL;	MA 55 years MBMI -	6 wks	Soy protein (25g/d)
Brink (2008)[17]	300 (63)	Amenorrhea 12-60 mos; FSH >20 IU/L; Non-osteoporotic; BMI 22-29 kg/m^2;	MA 53 years MBMI 24.5	12 mos	Soy protein (110 mg/d isoflavones)
Burke (2002)[18]	49 (7)	Age 18-48 years; Active menstruation; Non-complex migraine without aura; Migrain attacks >1 year; Migrain attacks/mos ≥3	MA 39.5 years MBMI -	28 wks	Combination (60 mg/d soy isoflavones; 100 mg/d dong quai; 50 mg/d black cohosh)
Campagnoli (2005)[19]	61 (14)	Age 45-58 years; BMI 18-28 kg/m^2; Surgical menopause or bilateral ovariectomy ≥3 mos or Amenorrhea >6 mos with E2 <30 pg/mL and FSH >40 IU/L; ≥5 HF/d	MA 51.5 years MBMI 24.5	12 wks	Soy capsules (60 mg/d isoflavones ± PUFA)
Cancellieri (2007)[20]	142 (17)	Postmenopausal; Age 45-65 years; No pharmacological treatment <30 d	MA 54.3 years MBMI 24.9	6 mos	Combination (Soy extract, red clover and black cohosh; 72 mg/d isoflavones)
Casini (2006)[21]	78 (2)	Intact uterus; Amenorrhea ≥12 mos; FSH >30 IU/L; E2 <10 pg/mL;	MA 49.5 years MBMI 24.6	6 mos	Soy Protein (60 mg/d isoflavones)
Chen (2003)[22]	203 (26)	Age 48-62 years; Amenorrhea ≥12 mos;	MA 54.2 years MBMI 24	12 mos	Soy extract (40 mg/d or 80 mg/d isoflavones)
Chiechi (2002)[23]	187 (58)	Amenorrhea ≥6 mos, FSH >30 IU/L and E2 <20 pg/mL or bilateral ovariectomy	MA 53.4 years MBMI 27.7	6 mos	Soy protein (47 mg/d isoflavones)
Colacurci (2005)[24]	60 (3)	Amenorrhea; No HRT (ever)	MA 55.2 years MBMI 25.9	6 mos	Tablets (60 mg/d isoflavones)
D'Anna (2005)[25]	90 (9)	Age 50-60 years; Amenorrhea ≥12 mos; FSH >50 IU/L	MA - MBMI -	6 mos	Tablets (54 mg/d genistein isoflavone)

Table 1 Continued

First Author (Year of Publication)	Participants (Withdrawn)	Inclusion Criteria	Participant Characteristics	Study Duration	Study Medication
Davis (2001)[26]	78 (23)	Non-asian women; Age 45-70 years; Lived in Australia ≥10 years; Amenorrhea ≥12 mos; FSH >25 IU/L; ≥14 HF/wk	MA 55.2 years MBMI 25.9	12 wks	Chinese medical herbs
Dodin (2005)[27]	199 (43)	Age 45-65 years; FSH ≥40 IU/L; Amenorrhea ≥6 mos; Normal mammogram <2 years;	MA 54.7 years MBMI 26.2	12 mos	40 g/d flaxseed
Faure (2002)[28]	75 (20)	≥7 HF/d; FSH >40 IU/L; E2 <35 pg/mL; HRT ex ≥6 wks	MA 53.5 years MBMI 24.9	4 mos	Soy extract (70 mg/d isoflavones)
Frei-Kleiner (2005)[29]	127 (15)	Age 45-60 years; ≥3 HF/d; ≥1 functioning ovary; climacteric disorders	MA 52.4 years MBMI 24.5	12 wks	C. racemosa (42 mg/d crude drug)
Gallagher (2004)[30]	65 (15)	Amenorrhea ≥12 mos or FSH >35 IU/L and E2 <30 pg/mL	MA 55.4 years MBMI 26.4	9 mos	Soy protein (96 mg/d or 52 mg/d isoflavones)
Gardner (2001)[31]	100 (6)	Amenorrhea ≥12 mos; Age <80 years; BMI 20-31 kg/m^2	MA 59.6 years MBMI 26	12 wks	Soy Protein (3 mg/d or 80 mg/d isoflavones)
Garrido (2006)[32]	29 (0)	Age 45-60 years; Amenorrhea ≥6 mos; FSH >20 IU/L; HRT ex >6 mos	MA 53.5 years MBMI 27	12 wks	Soy protein (100 mg/d isoflavones)
González (2007)[33]	32 (6)	NIDDM; Amenorrhea ≥12 mos	MA - MBMI 31	12 wks	Soy protein (132 mg/d isoflavones)
Hale (2002)[34]	32 (3)	Age 45-70 years; Amenorrhea ≥12 mos; HRT ex ≥6 mos; ≥6 mos no Antibiotics; ≥12 mos no smoking; BMI <35 kg/m^2	MA 57.3 years MBMI 24.9	2 wks	Soy protein (80 mg/d isoflavones)
Hallund (2006)[35]	23 (1)	Amenorrhea ≥24 mos; ≥6 mos no HRT; ≥3 mos no Antibiotics	MA 61 years MBMI 24.1	6 wks	Lignan Complex (500 mg/d)

Table 1 Continued

First Author (Year of Publication)	Participants (Withdrawn)	Inclusion Criteria	Participant Characteristics	Study Duration	Study Medication
Han (2002)[36]	82 (2)	Age 45-55 years; Amenorrhea ≥12 mos; ≥12 mos no HRT; intact uterus; FSH >25 IU/L; E2 <20 pg/mL; HF	MA 48.5 years MBMI 24.9	4 mos	(100 mg/d isoflavones)
Harkness (2004)[37]	20 (1)	Amenorrhea >8 years; Age >50 years; ≥3 mos no HRT	MA 70.6 years MBMI 25.9	6 mos	Soy protein (110 mg/d isoflavones)
Heyerick (2006)[38]	67 (12)	Age 45-60 years; Intact uterus; Amenorrhea ≥12 mos; ≥3 mos no HRT; 2-5 HF/d	MA 52.1 years MBMI 24.5	12 wks	Hop extract (100 μg/d or 250 μg/d 8-PN)
Hidalgo (2005)[39]	60 (7)	Amenorrhea >12 mos; Age >40 years; No HRT	MA 51.3 years MBMI -	90 days	Red Clover (80 mg/d isoflavones)
Hirata (1997)[40]	71 (10)	Amenorrhea ≥6 mos; Troublesome night sweats	MA 52.4 years MBMI 24.4	24 wks	Dong quai extract (4.5 g/d)
Ho (2007)[41]	200 (23)	Age 55-75 years; Amenorrhea ≥5 years; BMI 18-32 kg/m^2; ≥6 mos no HRT	MA 63.4 years MBMI 24.5	6 mos	Soy protein (80 mg/d isoflavones)
Ho (2007)[42]	203 (29)	Age 48-62 years; Amenorrhea ≥12 mos or <10 years	MA 54.2 years MBMI 24.1	12 mos	Soy protein (40 mg/d or 80 mg/d isoflavones)
Howes (2004)[43]	30 (2)	Age >60 years; Amenorrhea ≥5 years no HRT (ever)	MA 68.1 years MBMI -	6 mos	Rimostil® (Red Clover; 80 mg/d isoflavones)
Izumi (2007)[44]	26 (0)	Age 35-45 years	MA - MBMI -	12 wks	Soy protein (40 mg/d isoflavones)
Jacobson (2001)[45]	85 (16)	Age >18 years; ≤2 mos before treated for breast cancer (chemo-/radiotherapy)	MA - MBMI -	2 mos	C. racemosa
Jayagopal (2002)[46]	33 (1)	NIDDM; Amenorrhea ≥12 mos	MA 62.5 years MBMI 32.2	12 wks	Soy protein (132 mg/d isoflavones)
Katz (2007)[47]	25 (3)	Amenorrhea ≥12 mos; FSH >40 IU/L; E2 <25 pg/mL non-smoker; normolipidemic	MA 58.5 years MBMI 27.6	6 wks	Soy protein (55-65 mg/d isoflavones)

Table 1 Continued

First Author (Year of Publication)	Participants (Withdrawn)	Inclusion Criteria	Participant Characteristics	Study Duration	Study Medication
Khaodhiar (2008)[48]	191 (44)	Amenorrhea ≥6 mos; Age 38-60 years; ≥4 HF/d	MA 53.1 years MBMI 28.5	12 wks	Soft-gel Capsules (40 mg/d or 60 mg/d isoflavones)
Knight (2001)[49]	24 (4)	Amenorrhea ≥6 mos, FSH >40 IU/L or bilateral oopherectomy; Age 40-65 years; ≥3 HF/d	MA 53 years MBMI -	12 wks	TakeCare® (134.4 mg/d isoflavones, 77.4 mg/d aglycone)
Kotsopoulos (2000)[50]	94 (19)	Age 50-75 years; Amenorrhea ≥12 mos; FSH >20 IU/L; ≥12 mos no HRT; ≥3 mos no antibiotics; non-smokers; non-vegetarian	MA 59.5 years MBMI 25.5	3 mos	Soy protein (118 mg/d isoflavones)
Kreijkamp-Kaspers (2004)[51]	202 (49)	Age 60-75 years; ⊥mammogram <1 year; Amenorrhea	MA 66.6 years MBMI 26.2	12 mos	Soy protein (99 mg/d isoflavones)
Kumar (2002)[52]	97 (31)	Age 25-55 years; BMI <38 kg/m^2; no HT	MA 41.9 years MBMI 24.2	12 wks	Soy protein (40 mg/d isoflavones)
Lampe (2001)[53]	26 (6)	Age 20-40 years; regular menstrual cyclus; ≥4 mos no antibiotics; no HT	MA 32.1 years MBMI 23.3	1 mo	Soy protein (110 mg/d isoflavones)
Lewis (2006)[54]	99 (11)	Age 45-60 years; Postmenopausal ≥12 mos and <8 years	MA 53.1 years MBMI 27	16 wks	Flaxseed (50 mg/d lignans) or Soy Protein (42 mg/d isoflavones)
Lucas (2002)[55]	58 (22)	Postmenopausal; Age <65 years; no HRT	MA 54.5 years MBMI 28.9	3 mos	Flaxseed (40g/d)
Lydeking-Olsen (2004)[56]	107 (18)	Amenorrhea ≥12 mos; Age <75 years; ≥2 years no bone-active medication; ≥3 risk-criteria for osteoporosis;	MA 58.2 years MBMI 23.9	24 mos	Soymilk (76 mg/d isoflavones)
MacGregor (2005)[57]	72 (25)	Age >18 years; Histological confirmed pre-existing breast cancer; menopausal symptoms	MA 51 years MBMI -	12 wks	Soy capsules (70 mg/d isoflavones)
Maesta (2007)[58]	60 (14)	Amenorrhea ≥12 mos; FSH >40 IU/L; Age 45-70 years	MA 59.4 years MBMI 27.3	16 wks	Soy protein (50 mg/d isoflavones)
Martini (1999)[59]	40 (2)	Age 18-40 years; ≥6 mos no antibiotics	MA 26.3 years MBMI 23	2 mos	Soy product (38 mg/d isoflavones)

Table 1 Continued

First Author (Year of Publication)	Participants (Withdrawn)	Inclusion Criteria	Participant Characteristics	Study Duration	Study Medication
Maskarinec (2004)[60]	220 (31)	Normal mammogram no OC or HAT; intact uterus	MA 43 years MBMI 26	24 mos	Soy protein (50 mg/d isoflavones)
Maskarinec (2002)[61]	34 (5)	Age 35-46 years; ⊥mammogram <6 mos; ≥3 mos no OC or HAT; intact uterus; regular menstrual periods	MA 42.4 years MBMI -	12 mos	Soy protein (100 mg/d isoflavones)
Morabito (2002)[62]	90 (-)	Age 47-57 years; Amenorrhea ≥12 mos; FSH >50 IU/L; E2 <100 pmol/L	MA 51.7 years MBMI 23.7	12 mos	Tablets (54 mg/d genistein isoflavone)
Nahas (2004)[63]	50 (0)	Amenorrhea ≥12 mos; FSH >40 IU/L; HF; Contraindication or intolerance to HRT	MA 53.3 years MBMI 29	6 mos	Soy Germ (60 mg/d isoflavones)
Nahas (2007)[64]	80 (4)	Age ≥45 years; Amenorrhea ≥12 mos; FSH >40 IU/L; ≥5 HF/d	MA 55.1 years MBMI 29.1	10 mos	Soy extract (100 mg/d isoflavones)
Newton (2006)[65]	351 (45)	Age 45-55 years; Amenorrhea ≥12 mos; FSH >20 IU/L; ≥2 vasomotors symptoms per day	MA 52.2 years MBMI 28.6	12 mos	*C. racemosa* (160 mg/d) or MB + *C. racemosa* (200 mg/d) or MB + soy
Nikander (2003)[66]	62 (6)	Climacteric complaints; FSH >30 IU/L; Postmenonpausal	MA 54 years MBMI 23.6	3 mos	Soy protein (114 mg/d isoflavones)
Osmers (2005)[67]	304 (36)	Amenorrhea ≥12 mos or Amenorrhea ≥6 mos with FSH ≥50 IU/L; Age ≥45 years; Climacteric complaints	MA 53.5 years MBMI 25.2	12 wks	Remifemi® (*C. racemosa*; 2.5 mg/d isopropanolic)
Penotti (2003)[68]	62 (13)	Age 45-60 years; Amenorrhea ≥6 mos; LDL <160 mg/dL	MA 53.5 years MBMI 23.2	6 mos	Soy protein (72 mg/d isoflavones)
Pockaj (2006)[69]	132 (33)	≥14 HF/wk; history or increased risk of breast cancer	MA 66.4 years MBMI -	4 wks	*C. racemosa* (20 mg/d)
Quella (2000)[70]	177 (28)	Age >18 years; History of breast cancer (currently without evidence of residual malignant disease; ≥14 HF/wk;	MA - MBMI -	4 wks	Soy protein (50 mg/d isoflavones)
Rad (2006)[71]	24 (-)	BMI 19-29 kg/m^2; Age 46-65 years; Amenorrhea ≥12 mos	MA – MBMI 24.9	2 days	*C. racemosa* (50 mg/d, 250 mg/d or 750 mg/d 8-PN)

Table 1 Continued

First Author (Year of Publication)	Participants (Withdrawn)	Inclusion Criteria	Participant Characteristics	Study Duration	Study Medication
Reimann (2006)[72]	99 (10)	Age 45-70 years; Amenorrhea ≥12 mos; ≥6 mos no HRT; ≥3 mos no antibiotics	MA 59 years MBMI 24.4	8 wks	Soy protein (50 mg/d isoflavones)
Ritchie (2004)[73]	15 (0)	Age 30-51 years; Regular menstrual cycle	MA 41 years MBMI 22.9	6 mos	Soy protein 35 mg/d isoflavones)
Russo (2003)[74]	50 (3)	Age 48-54 years; Amenorrhea ≥12 mos and ≤3 years; neg. PAP test; ET ≤4 mm; Caucasian race; Climacteric complaints	MA 53.3 years MBMI 26.3	3 mos	Fitormil® (32 mg/d isoflavones)
Samman (1999)[75]	21 (7)	Age 18-45 years; Regular menstrual cycle; no HAT or OC	MA 27.5 years MBMI 21.3	2 mos	Red clover (86 mg/d isoflavones)
Sammartino (2003)[76]	70 (7)	Amenorrhea ≥12 mos; FSH >40 IU/L; E2 <20 pg/mL; ≥7HF/d	MA 51.8 years MBMI 25.3	12 mos	Fitogen® (36 mg/d isoflavones)
Sammartino (2006)[77]	80 (5)	Amenorrhea ≥6 mos and ≤2 years; FSH >40 IU/L; ≥7 HF/d; BMI 18-30 kg/m^2	MA 50.8 years MBMI 24.7	3 mos	Soy germ (60 mg/d isoflavones) andlignans (20 mg/d flaxseed) and *C. racemosa* (1.25 mg/d)
Schult (2004)[78]	252 (6)	Age 45-60 years; ≥35 HF/wk; Amenorrhea ≥6 mos or bilateral oopherectomy; FSH ≥30 IU/L	MA 52.3 years MBMI 26.2	12 wks	Promensil® (82 mg/d isoflavones) or Rimostil® (57.2 mg/d isoflavones)
Secreto (2004)[79]	262 (30)	Amenorrhea ≥6 mos; Age ≥35 years; ≥3 mos no HRT	MA 52.3 years MBMI 24.1	3 mos	Soy (80 mg/d isoflavones) or soy + melatonin or melatonin (3 mg/d)
Simons (2000)[80]	23 (3)	Age 50-70 years; Amenorrhea ≥12 mos; Non-smoking; Cholesterol <8 mmol/L; Triglycerides <3 mmol/L	MA 59 years MBMI 26.8	8 wks	Soy protein (80 mg/d isoflavones)
Sites (2007)[81]	18 (3)	Amenorrhea ≥12 mos and ≤5 years; FSH >30 IU/L	MA 55.6 years MBMI 30.5	3 mos	Soy protein (160 mg/d isoflavones)

Table 1 Continued

First Author (Year of Publication)	Participants (Withdrawn)	Inclusion Criteria	Participant Characteristics	Study Duration	Study Medication
Squadrito (2003)[82]	90 (11)	Age 52-60 years; Amenorrhea ≥12 mos; No surgical menopause; FSH >50 IU/L; E2 ≤100 pmol/L	MA 56.3 years MBMI -	12 mos	Genistein (54 mg/d)
Squadrito (2002)[83]	60 (0)	Age 52-60 years; Amenorrhea ≥12 mos; No surgical menopause; FSH >50 IU/L; E2 ≤100 pmol/L	MA 56 years MBMI -	6 mos	Genistein (54 mg/d)
St Germain (2001)[84]	80 (11)	Amenorrhea ≥12 mos; ≥10 HF/wk; ≥12 mos no HT; BMI 20-31 kg/m^2	MA 50 years MBMI -	6 mos	Soy Protein (4.4 mg/d or 80.4 mg/d isoflavones)
Steinberg (2003)[85]	42 (14)	Amenorrhea ≥12 mos; FSH ≥23 IU/L; ≥6 mos no HRT; BMI <30 kg/m^2	MA 54.9 years MBMI 24.6	6 wks	Soy protein (2 mg/d or 107 mg/d isoflavones)
Uesugi (2002)[86]	23 (0)	Age 40-62 years; perimenopausal	MA 54.1 years MBMI 22.7	4 wks	Soy protein (61.8 mg/d isoflavones)
Unfer (2004)[87]	376 (78)	Intact uterus; Amenorrhea ≥12 mos; FSH ≥30 IU/L	MA 49.5 years MBMI 24.6	5 years	Soy protein (150 mg/d isoflavones)
Upmalis (2000)[88]	177 (55)	Amenorrhea ≥6 mos; Age ≥50 years; FSH ≥30 IU/L; E2 ≤25 pg/mL; ≥5 vasomotor symptoms/d; ≥60 d no HRT	MA 54.8 years MBMI -	12 wks	Soy protein (50 mg/d isoflavones)
Van de Weijer (2002)[89]	42 (12)	Age 49-65 years; Amenorrhea ≥12 mos; ≥12 wks no HT or antibiotics	MA 53.4 years MBMI 25.6	12 wks	Promensil® (82 mg/d isoflavones)
Van Patten (2002)[90]	157 (34)	Amenorrhea ≥12 mos; ≥4 mos no HRT; ≥10 HF/wk; history of breast cancer (>4 mos since completion of treatment)	MA 55.2 years MBMI 26.7	12 wks	Soy protein (90 mg/d isoflavones)
Verhoeven (2005)[91]	124 (8)	Amenorrhea ≥6 mos; FSH >25 IU/L;	MA 53.9 years MBMI 25.5	12 wks	Soy extract (50 mg/d isoflavones) and*C. racemosa* (8 mg/d deoxyacetein) and primrose oil (1500 mg/d)

Table 1 Continued

First Author (Year of Publication)	Participants (Withdrawn)	Inclusion Criteria	Participant Characteristics	Study Duration	Study Medication
Vigna (2000)[92]	104 (27)	Amenorrhea ≥6 mos or Bilateral oopherectomy ≤6 wks; >7 HF/d; FSH >50 IU/L; E2 <130 pmol/L; ≥6 wks no HT	MA 53.4 years MBMI 25.9	12 wks	Soy protein (76 mg/d isoflavones)
Wiklund (1999)[93]	384 (5)	Age 45-65 years; ≥2 mos no HRT; Amenorrhea ≥6 mos	MA 53.5 years MBMI 25.8	16 wks	Ginsana® (100 mg/d ginseng extract)
Wu (2006)[94]	136 (8)	Age 45-60 years; Amenorrhea ≥12 mos and ≤5 years; no HRT or antibiotics	MA 54.6 years MBMI 21.7	24 wks	75 mg/d isoflavones
Xu (1995)[95]	7 (0)	Omnivorous; Good general health	MA - MBMI 22	3 days	Soymilk (3.4 or 6.9 or 10.3 μmol/kg/d isoflavones)
Xu (2000)[96]	18 (-)	Omnivorous; Good gerneral health	MA - MBMI 21.5	1 day	Soymilk (0.9 mg/d/kg isoflavones)
Ye (2006)[97]	90 (8)	Age 45-60 years; Amenorrhea ≥12 mos and ≤5 years; FSH >30 IU/L	MA 52.3 years MBMI 22.6	6 mos	Soy protein (84 mg/d or 126 mg/d isoflavones)
Zhang (2007)[98]	100 (15)	Amenorrhea 10-18 years; BMD 0.968-1.014g/cm^2 at lumbar spine	MA 63.5 years MBMI 23.8	24 mos	Epimedium-derived Phytoestrogen flavonoids (78 mg/d isoflavones)

FSH = follicle-stimulating hormone; E2 = estradiol; MA = mean age; HF = hot flashes; HRT = hormone replacement therapy; HT = hormone therapy; BMI = body mass index (kg/m^2); MBMI = mean body mass index (kg/m^2); LDL = low density lipoprotein; BMD = bone mineral density; PUFA = polyunsaturated fatty acids; NIDDM = non-insulin-dependent diabetes mellitus; 8-PN = 8-prenylnaringenin; OC = oral contraceptives; MB = multibotanical.