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Isoflavone supplements containing predominantly genistein reduce hot flash symptoms: a critical review of published studies

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ABSTRACT

Objective: Several reviews have evaluated the clinical evidence relating isoflavone treatment to the relief of menopausal hot flash symptoms. The majority of these reviews included a variety of isoflavone sources, often without discriminating between the identities of individual isoflavones contained in the study product. An evaluation of published studies using well-characterized isoflavone-containing supplements was conducted to determine whether the observed effects, or lack thereof, were attributable to differences in the composition of isoflavones in study products.

Design: Eleven studies that met the inclusion criteria were stratified according to specific isoflavone composition.

Results: All 11 studies contained similar total isoflavone doses. In five studies, involving a total of 177 treated participants, the study product provided more than 15 mg genistein (calculated as aglycone equivalents) per treatment. Each of these five studies consistently reported a statistically significant decrease in hot flash symptoms. In the six studies involving a total of 201 treated participants that provided less than 15 mg genistein per treatment, only one reported a statistically significant decrease in hot flash symptoms. Thus, the reduction in hot flashes was related to genistein dose, not total isoflavone content of the treatments.

Conclusion: Reports concluding that isoflavone supplements do not significantly reduce hot flash symptoms may be incorrect. The lack of discrimination between individual isoflavones contained in heterogeneous isoflavone mixtures from differing sources can be misleading when designing studies, interpreting results, and conducting reviews. In light of these observations, evaluation of isoflavone effects should focus greater attention to the specific composition within supplements in future studies.

Key Words: Isoflavone – Hot flashes – Menopause – Soy – Genistein – Daidzein.

Menopause is a gradual change in physiology, which is initially marked by a loss of menses and a decline in estrogen production. The accompanying changes in cardiovascular health, bone mineral density, and cognitive function are progressive with time. One of the symptoms that most perimenopausal and early postmenopausal women (75%-85%) experience is a feeling of intermittent intense heat, which is the classic symptom that accompanies menopause commonly known as a hot flash.[1,2] These spontaneous hot flashes result from a vasomotor response to declining estrogen levels. Hot flashes are often felt and seen as a redness of the upper face, neck, and torso created by peripheral vasodilatation, increased skin temperature, and increased blood flow.[2] These irritating vasomotor symptoms range in severity from a minor annoyance to a major disruption in the quality of life.[3] In the majority of women, hot flashes

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are thought to begin before menopause, and about 10% to 15% of women who have hot flashes have them very frequently and severely.[4] The period of time over which most women experience hot flashes is 6 months to 2 years,[4] but substantial numbers of women report having hot flashes up to 20 years after menopause.[5]

Most therapies designed to combat menopause-related hot flashes aim to restore hormone balance.[3] While estrogen therapy is an effective treatment for menopausal symptoms, many women are looking for alternatives because of concern over potential adverse effects of hormone therapy agents, which may include an increased risk of breast cancer, stroke, venous thromboembolism, and coronary heart disease (CHD).[3,6] One alternative to estrogen therapy that has been widely investigated is soy. Soy foods, containing isoflavones, are an integral part of many Asian diets and have received considerable attention in recent years for their potential role in reducing risk of CHD,[7] osteoporosis,[8,9] and certain cancers.[10,11] In addition, soy and isoflavones have been studied for the ability to alleviate hot flashes.[1] Generally, the incidence of hot flashes among women in Asia is lower than among North American and European women,[12,13] although many other menopausal symptoms (eg, shoulder aches, psychological changes) are experienced to a similar extent.[14] Soy foods and soy isoflavones have been adopted by some women as a natural alternative to hormone therapies because the soybean contains nutritionally relevant amounts of isoflavones.

Isoflavones belong to a class of compounds called phytoestrogens, which also includes coumestans and lignans. These phytochemicals are phenolic, nonsteroidal compounds that are structurally similar to estrogen and are known to interact with estrogen receptors in animals and humans (for review, see Branca and Lorenzetti[15] and Williamson and Manach[16]). Isoflavones are sometimes considered to be selective estrogen-receptor modulators, although there is some debate about this classification.[17] The weak estrogen-like effects of isoflavones were first proposed by Adlercreutz et al[18] in 1992 as a possible explanation for the low reported incidence of hot flashes experienced by women in Japan.[12,13]

Isoflavones are present at low levels in a variety of plant foods that are regular components in our diets, but are most abundantly found in soybeans.[15] Isoflavones consist of a large class of compounds; however, the three primary isoflavones found in soy are genistein, daidzein, and glycitein.[19] These three isoflavones are found in the soybean primarily derivatized as glycosides and are further conjugated with an attached acetyl or malonyl group.

Soy isoflavones are readily absorbed in the gastrointestinal tract, metabolized, and eliminated almost entirely within 24 to 36 hours after ingestion. Peak serum isoflavone levels typically occur between 3 and 7 hours post-ingestion.[20,21] There is variation in isoflavone metabolism and absorption among individuals, which can lead to variation in serum concentrations of parent isoflavones and their metabolites.[22,23] For example, approximately 30% to 40% of the general population in the United States possess gut microflora that convert the isoflavone daidzein to the more estrogenic dihydroxy isoflavan equol.[24] Equol has been proposed as an especially beneficial compound, and this conversion process may provide some added effectiveness from isoflavones for this particular subpopulation.[15,16,24,25]

Several reviews of clinical trials have examined the efficacy of alternative menopause treatments, including soy isoflavones, to alleviate vasomotor symptoms.[3,26,27] In addition, government agencies and health organizations have scrutinized the effect of phytoestrogens, particularly isoflavones.[28,29] In early 2005, a panel sponsored by the U.S. National Institutes of Health published an evidence-based Agency for Health Research Quality report concerned with menopause and treatment options. A portion of this report evaluated the use of dietary soy and isoflavones for the treatment of vasomotor symptoms.[30] Although reviews, panels, and government agencies have evaluated the clinical evidence relating isoflavone treatment to menopausal symptom relief, the majority of these evaluations include an expansive range of isoflavone sources collected under the heading of "phytoestrogens."[3,26-30] Often reviews fail to differentiate the chemical identity of individual isoflavone molecules contained in various study treatment products, other components in the specific source material, the compositional profile, or the specific quantities of individual isoflavones. An exception to this was the 2005 Agency for Health Research Quality report, which did segregate phytoestrogen sources in their evaluation. Soy sources were separated from other sources of phytoestrogens such as red clover and black cohosh, and soy isoflavones were further divided as either from dietary sources or from an extract.[30] However, this review did not take into account the specific amounts of the individual isoflavones genistein, daidzein, and glycitein contained in each study product.

Furthermore, a plethora of well-designed studies using similar treatment materials and matching patient populations does not exist for evaluating the effectiveness of alternative approaches for treatment of all menopausal symptoms. The Agency for Health Research Quality report summary noted for menopausal symptoms in general that "trials of soy isoflavones and other complementary and alternative medicine therapies report benefits in improving nonvasomotor symptoms, although results vary widely, methods are lacking, and studies are typically small and not generalizable."[30] Considering the breadth of isoflavone sources and the variation in study designs, substantial confusion exists about the effectiveness of isoflavones for treatment of menopausal symptoms. The general literature concerning the use of isoflavones is confounded by studies that either do not adequately describe the materials used to treat their participants, lack placebo controls, or were poorly designed (too few participants, too short of treatment duration). In this review of published studies, the literature was examined with these points in mind while specifically focusing on isoflavone supplements for the treatment of vasomotor symptoms associated with menopause.

This evaluation of the peer-reviewed literature focused specifically on studies that used well-characterized isoflavone-containing extracts to treat generally healthy postmenopausal women. Using this strategy, the observed effects, or lack thereof, could be attributable to specific isoflavones. The outcome focus was on the improvement of vasomotor symptoms, specifically hot flash symptom reduction. Studies that included women conjunctively using hormone therapy or tamoxifen were excluded. Studies in which vasomotor symptoms resulted from surgical menopause or cancer treatment were also excluded. The purpose of this review was to evaluate the scientific support for the efficacy of soy isoflavone extracts for the relief of hot flash symptoms caused by the natural onset of menopause.

METHODS

Published studies were identified by searching the National Library of Medicine; PUBMED (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db= PubMed), Chemical Abstracts, and Nerac databases (www.nerac.com). Search terms included soy, phytoestrogen, isoflavone, hot flash, and menopause. The primary study selection criteria included reports concerning isoflavone extract treatment of hot flashes (either solely or in conjunction with other menopausal symptoms), and in early postmenopausal women who were otherwise healthy women. We purposefully restricted this review to published studies to include completed and peer-reviewed work.

Eligible studies used semipurified isoflavone extracts, not in combination with other herbal extracts, administered as a dietary supplement and compared to a placebo treatment or control group. Only trials that used isoflavones derived from soy were included. Studies that used dietary soy sources (foods, shakes, and protein powders) to provide isoflavones were excluded because of the nonquantitated presence of other matrix compounds. Red clover isoflavone extracts were excluded because they contain predominantly formononetin and biochanin A. Although in vivo conversion of these isoflavones to daidzein and genistein, respectively, is well-known, variation in individual metabolism can confound the analysis with respect to effective agent form. The conversion rate varies among individuals, thereby preventing accurate assessment of genistein, daidzein, and potentially equol exposure. Studies were excluded that involved women who were surgically menopausal or cancer patients currently treated with other estrogen-like compounds or drugs.

The studies were stratified in relation to their specific isoflavone composition and the amount of genistein in the supplement. Study results and statistical significance were accepted as reported in the paper and were used to classify the findings as positive ($P < 0.05$) or as no effect of treatment ($P > 0.05$). The principal measure of effect was the reduction in hot flash occurrence; however, three of the included studies used menopausal indexes such as the Kupperman Index and Greene's Climacteric Score to evaluate effects on overall menopausal symptoms.[31-33] These studies did separate evaluations of hot flash severity, but did not have their participants record daily quantities of hot flash occurrence.

To establish a common basis for direct comparisons, all study treatment compositions were normalized to their calculated aglycone isoflavone equivalent; these recalculated isoflavone doses were expressed as milligram aglycone equivalents for each of the isoflavones. Thus, isoflavone glycosides were calculated as their aglycone equivalents by weight[34] and are presented as such throughout this review. When the composition and amount of isoflavones in a particular study were not clearly presented, authors were contacted to determine the specific amount of isoflavones in each treatment. If the authors could not be reached, the composition of the study material was obtained either

from public information or by independent analysis of commercially available products used in the study. Analyses for isoflavone content of products was performed using methods previously described by Griffith and Collison.[35]

RESULTS

Our systematic searches revealed 21 published studies using isoflavone supplements that met the primary study criteria. Five of these studies were excluded based on their use of red clover isoflavones.[36-40] Two studies were excluded because the soy isoflavones were combined with another plant extract.[41,42] The remaining 14 studies used soy extracts; however, two of these studies were excluded because some of the participants were simultaneously treated with tamoxifen.[43,44] One study was excluded because it did not include a control group.[45] The remaining 11 studies met the inclusion criteria.[31-33,46-53] We believe the quality of these included studies to be generally good.

The 11 studies evaluated in this review lasted from 12 weeks to 1 year in duration (Table 1). Eight studies were conducted as a parallel design, whereas the remaining three studies used a crossover design (Table 1). On average, participants were 52.2 years of age, experienced from four to 10 hot flashes per day (Fig. 1), and were established as postmenopausal by lack of menses for at least 6 months. In addition, eight of the studies used serum levels of follicle-stimulating hormone and estrogen as hormonal criteria to establish menopause. There were 745 women in total who participated in these studies; 378 of the women (50.7%) were treated with isoflavones; each study had 13 to 63 participants treated with isoflavones (Table 1).

Baseline hot flash occurrence data are presented in Figure 1. However, three of the 11 studies did not provide baseline hot flash occurrence data; thus, these studies were omitted from Figure 1. Approximately five hot flashes on average were reported in all the studies providing baseline hot flash data. Messina and Hughes[54] have suggested in their analysis that isoflavone efficacy is positively related to baseline hot flash frequency, and reductions occurred primarily in studies involving women who on average had at least five hot flashes per day.

The studies in Table 1 are grouped according to the amount of calculated genistein provided per treatment. A 10- to 15-mg genistein threshold created a natural grouping of studies, with similar dose ranges of total isoflavones (Fig. 2A), but different levels of genistein (graphically depicted in Fig. 2B), thus separating the papers by "low" and "high" genistein content (Table 1). Five of the studies, involving 177 participants, used isoflavone treatments that provided greater than the equivalent of at least 15 mg genistein per treatment (Table 1). All five of these studies consistently reported a statistically significant decrease in hot flashes. The remaining six studies (201 treated participants) used an isoflavone treatment that was relatively (<10 mg) low in genistein.

The total isoflavone exposure ranged from 30 mg aglycone isoflavone equivalents per day to 114 mg aglycone isoflavone equivalents per day. The low- and high-genistein groups had similar distributions of

TABLE 1. *Characteristics of studies and participants*

Study	Design	Duration (wk)	Total aglycone isoflavone supplementation (mg/d)	Total genistein supplementation (mg aglycone/d)	Composition origin and ratios (genistein/daidzein/glycitein)	Age, y	Control/ placebo (n)	Soy isoflavone treatment (n)	Reported significant effect (*P*)
Low genistein-containing soy isoflavone supplements									
Campagnoli et al[46]	Crossover	12	38.4	5.8	Soy cotyledon (1:1:?)	51	29	29	NS
Faure et al[47]	Parallel	16	42	5	Soy germ (0.2:1:0.4)	53	35	38	NS
Nahas et al[48]	Parallel	24	36	5	Soy germ (16% Gen)	53	25	25	<0.05
Nikander et al[31]	Crossover	12	114	8	Soy germ (0.2:1:1.6)	52	28	28	NS
Penotti et al[49]	Parallel	24	60	9	Soy germ (0.3:1:0.7)	52	34-27	28-22	NS
Secreto et al[32]	Parallel	12	48	7	Soy germ (0.3:1:0.7)	52	58	59	NS
Total							202	201	
High genistein-containing soy isoflavone supplements									
Colacurci et al[50]	Parallel	12	70	50	Soy cotyledon (2.5:1:?)	52	13	13	<0.01
			105	75				15	<0.03
Crisafulli et al[51]	Parallel	52	54	54	Pure genistein	52	30	30	<0.05
Han et al[33]	Parallel	16	100	70	Soy cotyledon (3.7:1:0.6)	49	40	40	<0.03
Scambia et al[52]	Parallel	6	30	15	Soy cotyledon (1.5:1:0.5)	54	19	20	<0.01
Upmalis et al[53]	Parallel	12	30	15	Soy cotyledon (1.0:1:0.0)	54	63	59	<0.05
Total							165	177	

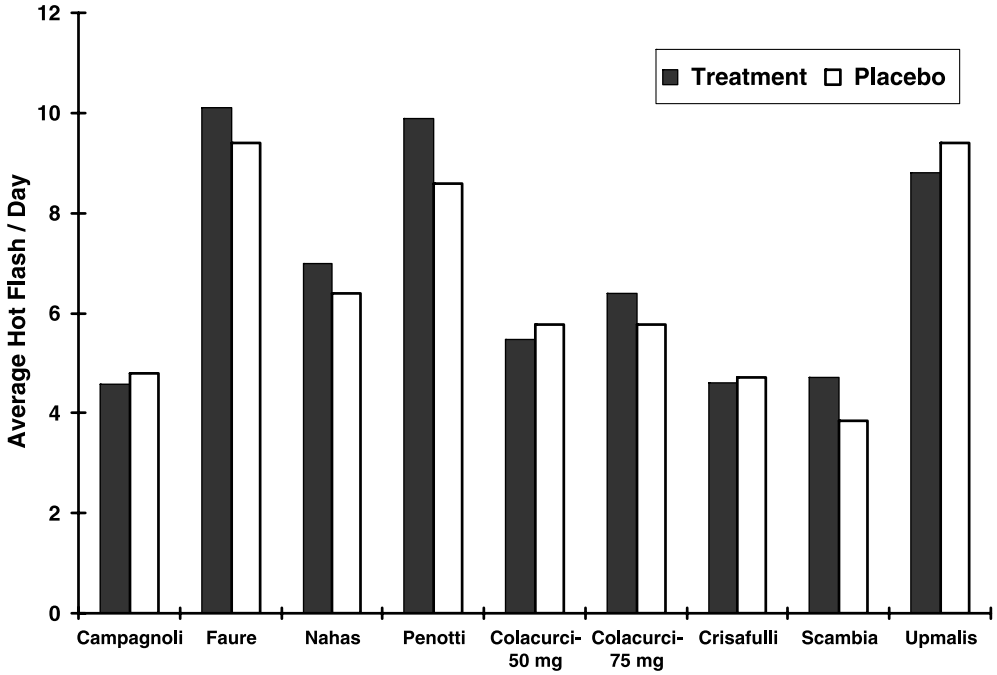

FIG. 1. Initial hot flash occurrence and number of participants. Solid bars represent the average number of daily hot flashes in the treatment group. Open bars represent the average number of daily hot flashes in the control group.

total isoflavone doses (Fig. 2A). The average total isoflavone treatment overall for the high- and low-genistein groups was 64.8 mg and 56.8 mg, respectively. In contrast, Figure 2B illustrates the differences in genistein intake in these two groups, each averaging 40.8 and 6.6 mg genistein per day, respectively.

Genistein level and a report of a significant decrease in hot flash were related. Figure 3 clearly shows the genistein dose amount for each study. All of the low-genistein studies used treatments containing less than 10 mg genistein per day with the remainder of the total being made up of daidzein and glycitein. Five of the six low-genistein treatments were not successful at reducing hot flash symptoms compared to control, as indicated by their reported statistics, independent of the total isoflavones administered (Table 1 and Fig. 3). In contrast, all five of the studies using more than 15 mg of genistein in their treatment groups consistently reported a significant reduction of hot flashes, indicated by the asterisks in Figure 3 and listed in Table 1. Thus, a treatment regimen of less than 10 mg genistein is generally unsuccessful at reducing hot flash symptoms. This effect does not appear to be related to the total dose of isoflavones used in the studies (Fig. 3). Therefore, the amount of genistein present in the dose appears to be important for the treatment for hot flashes, whereas the total isoflavone exposure is unrelated to efficacy. This is exemplified in Figure 3 where, on a percentage basis, genistein ranged from 7% to 16% of the total isoflavone treatments used in the low-genistein studies (Fig. 3), while in the high-genistein studies the amount of genistein was 50% to 100% of the isoflavone treatment material used.

DISCUSSION

The present review demonstrates a distinct division in effectiveness of isoflavone extracts to treat hot flashes in postmenopausal women. We observed that soy isoflavone supplements that provide at least 15 mg genistein per day are effective at alleviating hot flash symptoms, whereas those providing less than 10 to 15 mg are not. This clear distinction became apparent by examining specific isoflavone molecule content and not the broadly inclusive value of total isoflavones. These obvious results imply that the conclusions of previous reviews suggesting lack of effectiveness of isoflavones for reduction of hot flash symptoms may be misleading due to the broad inclusion of all studies using "phytoestrogens" with this heterogeneous class of compounds. The strength of this review is the narrow inclusion of studies using specific, known combinations of soy isoflavones. A potential weakness is that we did not have access to the original data for each study that could be used to do a complete meta-analysis or further efficacy

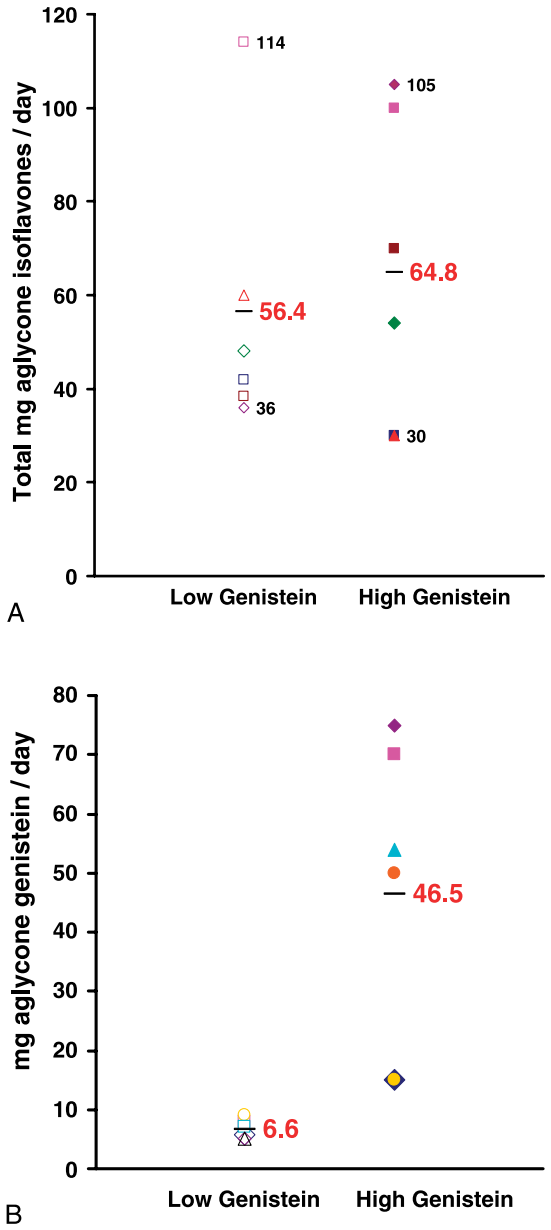

FIG. 2. **A, B:** Dose ranges for the included studies. Open shapes represent studies in the low-genistein (<10 mg) treatment group, and filled shapes represent studies in the high-genistein (>10 mg) treatment group. Averages are marked with a solid bar. **A:** The total isoflavone treatments. **B:** Only the genistein content of the treatment.

analysis measures. Also, each of the studies varies in design, length of treatment, and treatment materials, thus limiting the ability to pool the data to look at the effect across all studies. Krebs et al[26] encountered a similar challenge in their review.

Within the various papers using high-genistein supplements, the study reported by Colacurci et al[50] was a randomized trial with parallel comparison between one of two oral doses of soy isoflavones and a nontreated control. This study also included a topical treatment of isoflavones, although we did not include these results in our evaluation. Only one study used isolated genistein (54 mg/d) and the results suggest that genistein exposure alone, without accompanying intake of daidzein or glycitein isoflavones, is efficacious.[51] This may not be true for other nonvasomotor menopausal symptoms (eg, bone loss), where a combination of soy isoflavones may be more effective than genistein alone. However, additional research or review is required before such conclusions can be made.

The studies with modest dose levels of genistein provide insight into the threshold genistein intake value required for the alleviation of hot flash symptoms. The 6-week study by Scambia et al[52] found 15 mg genistein (total isoflavones, 30 mg) was highly effective in reducing hot flashes compared to a placebo control. This study demonstrated the minimal amount of genistein needed to reduce hot flash occurrence and is further supported by the study published by Upmalis et al.[53] The studies published by Han et al[33] and Colacurci et al[50] show the effectiveness of supplements with even greater levels of genistein in treating hot flash symptoms in postmenopausal women.

In contrast to the five studies using high-genistein containing treatments, only one of the six studies using low-genistein supplements reported a statistically significant reduction in hot flash symptoms when compared to a placebo control.[31,32,46,47,49] Only the one study by Nahas et al[48] with 30 participants treated with a soy germ product containing only 5 mg genistein reported an effective reduction in hot flashes. However, the balance of the evidence from these studies shows the ineffectiveness of treatments containing less than 10 mg genistein.

Interestingly, soy germ products are derived from the soy hypocotyledon, which comprises only approximately 2% of the whole soybean,[55] whereas the soy cotyledon products are derived from more than 90% of the whole soybean.[55] Soy germ products are naturally low in genistein content, whereas soy cotyledon products are naturally higher in genistein content.

In this review, the original data from each study were not re-evaluated. All results were taken from the reported changes presented in the 11 peer-reviewed reports. This could be considered a weakness of this report, as we relied on the statistical evaluations reported in each paper to assess value to the isoflavone treatments. However, it is unlikely that prior knowledge of genistein content of the

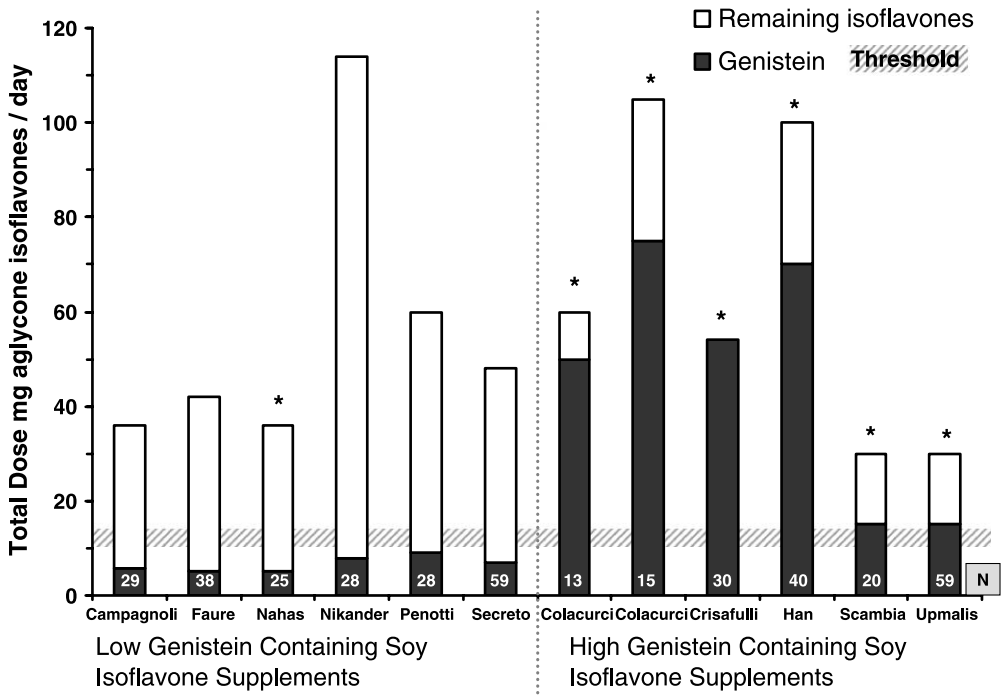

FIG. 3. Isoflavone doses. Genistein treatment amounts (solid columns) are shown in relation to the nongenistein isoflavone (open columns) content of the treatment materials. Effective treatments included greater than 15 mg genistein per day. Low- and high-genistein grouped reports separated by vertical dashed line. Numbers at the base of the bar indicates the number for the treatment group. The number of treatment and control participants is also listed in Table 1.

products would have influenced the statistical outcomes of these papers. Furthermore, the quality of the study design was considered, but not restricted solely to the absolute gold standard, although each of the studies was conducted as a randomized, controlled trial. In the end, however, the literature did reveal a very consistent message that treatments containing 15 mg genistein or greater significantly reduced the occurrence and severity of hot flashes.

Isoflavone extracts can vary considerably in their isoflavone profile; hence, any research using isoflavone or phytoestrogens needs to fully characterize the material used, state the source of that material, and report the material in a specific, standardized way that other researchers can easily understand and reference when designing future studies. In this critical review, careful identification of the treatment materials and of the extract contents in a normalized comparable fashion was undertaken. If future reports use this fashion of specifically reporting the isoflavone content of the treatments, the body of scientific information would be more easily compared and understood.

In summary, the previous reports finding an inconclusive relationship between isoflavone consumption and hot flash reduction suffer from overgeneralization by including any product using the term "isoflavones." Therefore, a lack of discrimination and quantification between individual molecular entities contained in heterogeneous isoflavone sources can lead to misinterpretation of the data. The use of isoflavone supplements to treat menopausal hot flashes should be undertaken with the consideration that extract products using a higher genistein ratio and containing a minimum genistein dose level are more effective at reducing hot flashes. Furthermore, evaluations of isoflavone effects should be related to content of individual isoflavones within supplements.

CONCLUSIONS

Isoflavone extracts, which contain isoflavone profiles similar to what is found in soy foods, that meet a minimum threshold of 15 mg genistein per day can be effective in reducing the frequency and severity of hot flashes. Future research should be mindful of this perceived threshold of 10 to 15 mg genistein per day as effective for the treatment of hot flash symptoms. Also, future studies examining the effectiveness of isoflavones for other menopausal symptoms should be conducted with greater thoroughness and greater attention to doses of

individual isoflavone components, to placebo controls, and to improved patient monitoring. Additional studies examining the sources of isoflavones (germ versus cotyledon) and their doses of genistein may prove insightful in the future to directly support the empirical findings of this review.

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