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Effects of Isoflavones and Amino Acid Therapies for Hot Flashes and Co-occurring Symptoms during the Menopausal Transition and Early Post Menopause: A Systematic Review

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Abstract

Aims—Review controlled clinical trials of isoflavones and amino acid preparation effects on hot flashes and at least one other symptom including mood, sleep, pain, and cognitive function that women report during the menopausal transition and early postmenopause.

Methods—An experienced reference librarian searched PubMed/Medline, CINAHL Plus, PsycInfo, Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, Web of Science, EMBASE, AMED, and Alt-Health Watch for English-language randomized controlled trials between 2004 to July 2011. Seventeen trials of isoflavones and amino acid effects on hot flashes and one additional symptom were identified.

Results—In five trials of soy isoflavone preparations, two (6g soy germ extract and 25g soy protein in soy nuts) significantly decreased hot flashes, but no other symptoms. In the seven trials

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of other isoflavones, six significantly reduced hot flashes; in addition, Red Clover (80 mg) significantly reduced mood symptoms; Rexflavone (350 mg) for women with Kupperman Index > 20 significantly reduced sleep symptoms; two trials had significant reductions for pain: Isoflavone powder (90 mg) and Red Clover (80 mg). The only trial in this systematic review that significantly reduced cognitive symptoms was Red Clover (80 mg). In one trial, Red Clover isoflavone (80 mg/d) significantly relieved hot flashes, mood, pain, and cognitive symptoms. Amino acids yielded no significant results. Equol supplements of 30 mg/d for non-Equol producing women significantly reduced mood symptoms in one trial. The Magnolia Bark Extract combination significantly reduced hot flashes, mood, and sleep symptoms.

Conclusions—Isoflavone trials yielded significant reductions on hot flashes and co-occurring symptoms during the menopausal transition and postmenopause, but studies require replication with larger sample sizes and attention to measurement of outcomes.

Introduction/Background

Since the publication of the Women's Health Initiative Study in 2002[1], complementary and alternative therapies have generated interest among those who are seeking treatment modalities other than hormone replacement therapy (HRT) for menopausal transition-related symptoms. Soy is a staple in many Asian diets and is consumed in greater quantities in Asian countries than in the United States. The incidence of hot flashes is 18% in China, 15% in Japan, and 14% in Singapore compared to 80-85% in European and American women[2,3], and 70% of Brazilian women[4]. The estimation of daily intake of soy isoflavones in Asian women is approximately 50-100 mg/dl compared to <1 mg/dl in Western women[5,6].

In one recent review[7], Guttoso used evidence-based methodology to mirror the FDA (US Food and Drug Administration) and EMEA (European Medicines Agency) guidelines as a template to identify “well designed” random controlled trials. Of the 14 well-designed trials using soy-derived isoflavones, three demonstrated a clinically meaningful benefit for the relief of hot flashes (HF). A clinically meaningful benefit, according to the EMEA, is a reduction of at least 2 fewer HF/day than placebo. None of the 5 well-designed red clover trials demonstrated a significant or clinically meaningful benefit for the relief of hot flashes. Further, the review supported the idea that higher concentrations of the isoflavone, genistein, may be more effective in the relief of hot flashes. Through a meta-analysis and systematic review of extracted or synthesized soybeans, Taku et al.[8] found that soy isoflavones (median 54 mg) taken for 6 weeks to 12 months significantly reduced hot flash frequency by approximately 21 % and hot flash severity by approximately 26% compared to placebo. And further, isoflavone supplements that provided more than 18.8 mg of genistein were more than twice as potent at reducing hot flash frequency than lower genistein supplements. Eden's review[9] reported that meta-analyses of random controlled trials of isoflavones for the relief of ‘menopausal flushing’ have consistently failed to show a therapeutic effect. Eden further explained that the authors who performed the meta-analyses commented on the heterogeneity of the studies, the different composition of the isoflavones, and suggested that treatment for ‘menopausal flushing’ with isoflavones was difficult to recommend. Villaseca[10] concluded that phytoestrogen efficacy on vasomotor symptoms was similar to

placebo. Another review[11] determined that there was no robust evidence of red clover isoflavones on vasomotor symptoms, in particular, hot flashes.

Recent reviews on soy and isoflavones for the relief of menopausal transition symptoms have included only one symptom: hot flashes. To date, there are no published systematic reviews of soy, isoflavones, and amino acids therapies for hot flashes and co-occurring symptoms such as mood disturbances, sleep disruption, pain, and cognitive dysfunction.

Cray et al.[12] found that women experience menopausal transition symptoms in clusters. By using Latent Class Analysis in a different study, Cray and colleagues[13] determined that there are at least three clusters. One cluster included high severity hot flashes and low severity symptoms of mood, sleep, pain and cognition; a second cluster included low severity hot flashes with moderate symptoms of mood, sleep, pain, and cognition; and the third cluster consisted of low severity hot flashes, with low symptoms of mood, sleep, pain, and cognition. Much of the menopausal transition symptom management literature focuses on one symptom, hot flashes. Since women usually report more than one symptom during the menopausal transition, the purpose of this study was to systematically review trials of isoflavones and amino acids that studied hot flashes and at least one other symptom: alterations in mood, disturbances in sleep, pain, or cognitive dysfunction.

Methods

This review included original, published reports of studies that involved multiple symptoms such as hot flashes as treatment outcomes, with primary and secondary outcomes. In addition to hot flashes, four groups of symptoms co-occurring with hot flashes were investigated. Co-occurring symptoms means at least one other symptom group occurred at the same time as hot flashes in the same study. The co-occurring symptom groups and their representative symptoms were MOOD disturbances (depressed mood, depression, mood changes, melancholia, anxiety, crying or irritability), SLEEP disturbances (early awakening, difficulty going to sleep, awakening at night or insomnia), PAIN (joint pain/aches, headache, backache/pain or arthralgias/myalgias) and COGNITIVE disturbances (forgetfulness, problems concentrating or poor memory). The symptom groups and their representative symptoms were based on prior principle components analysis[12,13].

Procedure

An extensive search of PubMed/MEDLINE (National Library of Medicine), CINAHL Plus (Cumulative Index to Nursing and Allied Health Literature EBSCO), PsycInfo (EBSCO), Cochrane Database of Systematic Reviews (Wiley), Cochrane Central Register of Controlled Trials (Wiley), Web of Science (Thomson Reuters), Embase (Elsevier), AMED (Allied and Complementary Medicine Database-EBSCO), and Alt HealthWatch (EBSCO) for randomized controlled trials reported in English between January 2004 to July 6, 2011 was conducted by an experienced reference librarian, Janet G. Schnall. The extensive initial search strategy was for a large systematic review that was divided into four different kinds of nonpharmacological or alternative medical treatments to hormone therapy for menopausal transition symptoms. The four kinds of nonpharmacological/alternative medical treatments

were 1) Mind/Body Therapies[14], 2) Herbal Therapies, 3) Isoflavones and Amino Acid Therapies, and 4) Accupuncture and Traditional East Asian Medicine Therapies. This manuscript reported on the Isoflavones and Amino Acid Therapies.

The search strategy yielded 1193 abstracts. Based on this review process, 58 unique trial reports were identified that met the inclusion and exclusion criteria of the study. Of these, 17 focused on herbal preparations, 17 on isoflavones/amino acids, 14 on Traditional Chinese Medicine, and 10 reports of 8 trials of mind-body interventions. This review focused on the 17 trials with isoflavones or amino acids. The description of the electronic search method and research strategy was previously published[14].

Measures

Symptoms

A variety of measures was used by the studies in this paper to determine symptom outcomes, including: hot flash diaries, hot flash checklists, Greene Climacteric Scale (GCS) and subscales [32], the Kupperman Index (KI) [33], Menopause Rating Scale (MRS) [34], Menopause Symptom Scale for Japanese women and subscales[35], Menopause specific quality of life (MENQOL) [36,37], Simplified Menopausal Index (SMI) and subscales [38], Pittsburgh Sleep Quality Index (PSQI) and subscales [39], Profile of Mood States (POMS) and subscales[40-42], the Identical Pictures test[43], the Verbal Fluency test[43], and the Trail Making test[44]. The results reported were analyzed to determine if they included the five symptom groups and/or one or more of the 17 representative symptoms that comprised the symptom groups. (See Appendix 1 for a summary of measures accepted as indicators in this review).

Isoflavone and amino acid therapies

As seen in Table 1, the soy isoflavone interventions consisted of soy protein powder (20g), soymilk (12.5g), soy germ extract (6g), soy nuts (25g), and soy flour muffins (25g). The controls/comparisons for the soy protein category were whole milk protein, roasted wheat powder, The Lifestyle Change (TLC) Diet, ground flaxseed muffins, and wheat flour muffins.

The other isoflavone category interventions used synthetic genistein (30mg), isoflavone powder (90 mg), Rexflavone (350mg), genistein (90mg), and red clover (80mg), 35 mg and 70 mg isoflavones, and 40 mg isoflavones. The controls/comparison groups for the isoflavone category were microcrystalline cellulose placebo capsules, maltodextrin placebo tablets, and lactose packets.

The amino acids interventions included methionine (2g) and L-isoleucine (5g). The methionine control consisted of cornstarch and microcellulose and the L-isoleucine control was not described.

There were 3 studies in the isoflavone combinations category in which isoflavones were combined with other substances. EQUOL in 10 mg or 30mg doses; a composition of Magnolia bark extract, soy isoflavones, lactobacillus, calcium, Vitamin D; and one consisting of isoflavones (80mg) with melatonin (3mg). For the isoflavone combinations

category, the control/comparison groups were lactose packets, calcium (141mg) and Vitamin D (5 μg) tablets, and sorbitol, respectively.

Analysis

Data were analyzed by reviewing patterns of effects on individual symptoms and co-occurring symptoms for the therapies included in the studies. Table 1 includes data extracted from all 17 trials. Table 2 shows a summary of significant between-group treatments for isoflavones and amino acids on hot flashes and associated symptoms. Table 3 identifies adverse events reported in the studies reviewed.

Results

This review focuses on a total of 17 papers related to the effects of soy isoflavones, other isoflavones, isoflavone combinations, and amino acids, representing a total of 1404 participants in 17 trials from 10 countries. There were four categories of interventions: soy isoflavones[15-19], other isoflavones[20-26], isoflavone combinations[27-29], and amino acids[30-31].

Soy Isoflavones

As seen in Table 2, only 2[17,18] of the 5 soy agents significantly reduced hot flashes and none of them provided evidence of significantly reduced mood, sleep, pain, or cognitive disturbances. Soy germ extract (6 g)[17] significantly relieved hot flashes, but only in EQUOL-producing women[17]. Soy nuts (25g soy protein)[18] significantly reduced hot flashes. (See Table 2).

Other Isoflavones

Other isoflavones significantly reduced hot flashes in all but one study[25]. The interventions effective for hot flashes were (in order of Table 2) synthetic genistein (30mg)[20], 90mg isoflavone powder[21], Rexflavone (350 mg)[22] for women whose Kupperman Index (KI) was greater than 20, Genistein (90 mg)[23] for women whose Greene Climacteric Score (GCS) was greater than 9, Red Clover (80mg)[24] and 40 mg isoflavones[26] for women whose Simplified Menopausal Index (SMI) was greater than 26. Only one trial[24] showed significant reduction in hot flash frequency, depression, arthralgia and headaches, and lack of concentration using 80 mg Red Clover[24]. Sleep disturbances were not assessed nor were subscales reported in 11 of 17 studies; None of the studies in the other isoflavone category indicated a significant reduction in sleep symptoms. Pain symptoms were not assessed or reported in the majority of studies, but in the 6 studies[16,17,21,22,24,26] in which pain data were available, 2 trials[21,24] showed a significant reduction in joint/muscle pain, headaches and/or arthralgia. The interventions that significantly reduced hot flashes and co-occurring pain symptoms were in the other isoflavones category: isoflavone powder (90 mg dose)[21] and red clover (80 mg)[24]. Cognitive symptoms such as forgetfulness, problems concentrating or poor memory were not assessed or reported in the majority of studies. In the 3 studies[15,16,24] in which cognitive symptoms were reported, only red clover[24] (80 mg) showed a significant decrease in hot flashes and a significant improvement for lack of concentration.

Isoflavone Combinations

Thirty milligrams of EQUOL in Non-EQUOL producing women[27] provided significant relief of mood (anxiety) symptoms alone[27]. A combination[28] of magnolia bark extract (60mg), magnesium (50mg), isoflavones (60mg), lactobacillus (500 million spores), calcium (141mg) and Vitamin D3 (5μg) was the only therapy in this category that significantly reduced hot flashes, with the disappearance rate of hot flashes by week 2, and also significantly reduced mood symptoms (irritability, anxiety and depression).[28] Only this preparation[28] significantly reduced insomnia.

Amino Acids

Neither of the amino acid trials[30,31] yielded significant results for any of the symptoms.

Discussion

Based on this review, women who have hot flashes and at least one other co-occurring symptom may benefit from the use of certain isoflavone therapies. For women who have hot flashes and the co-occurring symptoms of irritability, anxiety, depression and insomnia (hot flashes, mood, and sleep), the isoflavone combination[28] of Magnolia Bark extract (60mg), magnesium (50mg), isoflavones (60mg), lactobacillus (500 million spores), calcium (141mg) and Vitamin D3 (5μg) produced significant reduction of symptoms[28]. Red clover (80 mg)[24] significantly reduced symptoms in women who suffered from hot flashes, depression, arthralgia, headaches, and lack of concentration (hot flashes, mood, pain, and cognition) [24]. Ninety milligrams of isoflavone powder[21] significantly reduced hot flashes and joint pain symptoms[21].

None of the soy isoflavones tested improved hot flashes and at least one co-occurring symptom; only two interventions[17,18] improved hot flashes alone[17,18]. Two trials[21, 24] in the other isoflavones category significantly reduced hot flashes and at least one co-occurring symptom. Only one of the isoflavone combinations[28] significantly decreased hot flashes and two other co-occurring symptoms.

The challenge of managing multiple co-occurring symptoms with isoflavones will require additional study to address limitations in this literature. Most studies enrolled limited numbers of participants, thus limiting power to detect effects. Only one study included more than 100 participants[29]. In addition, no two trials used the same composition and doses of isoflavones, therefore making it impossible to see significant reductions across multiple trials of the same agent and dose.

Given the importance of producing EQUOL in the metabolism of Diadzein, one of the components of isoflavones, determining the status of trial participants as EQUOL producers was important to interpretation of effects. Non-Equol Producing women (Non-EP) may not benefit from soy or isoflavones because they may lack the enzyme or bacterium in their intestine that converts Diadzein into Equol, which resembles 17β-estradiol, and has a higher affinity for both estrogen-binding sites in blood vessels. Five[17,19,23,26,27] of the 17 studies in this systematic review reported whether or not women were Equol Producers (EP). Effects of isoflavones differed for women who were EP and non-EPs. For example, in one study[17]

of 6g of total soy protein, which is 135 mg isoflavone (Genistein 17.1 mg, Diadzein 65.4 mg, Glycitein 52.5 mg), Jou et al.[17] reported significant hot flash reduction at 3 months in EP women only, using the Kupperman Index (KI) scale. In another, Lewis et al.[19] reported that only 9 subjects or 39% of their soy arm subjects were EPs and that using 42mg per day of isoflavones (Genistein 25.7 mg, Diadzein 15.5 mg, Glycitein 0.7 mg) produced no significant results for quality of life or hot flash frequency/severity using the MENQUOL scale. Most of the women in their soy arm (61%) were not Equol producers. One possible conclusion would be that EP women are able to use isoflavones rich in Diadzein to produce equol, which has a high affinity for the estrogen binding sites, and thus would experience reduced hot flashes and/or co-occurring symptoms. Since non-EP women may not benefit by using soy isoflavones or other isoflavones because they lack the gut micoflora to convert Diadzein into equol, they may benefit by an equol (30 mg)[27] supplement that binds to the estrogen receptor site.

Some trials suffered from inclusion criteria that did not specify sufficient levels of severity or frequency of symptoms. To address this, some investigators[22,23,26] conducted analyses of subgroups of women with higher vasomotor scores than the rest of the group (e.g., Kupperman Index > 20, Greene Climacteric Scale > 9, and Simplified Menopausal Index > 26) resulting in limited power (less participants) to detect between group differences.

Another methods challenge was the inability to distinguish women's treatment responses based on whether they were in the menopausal transition stages or in the early postmenopausal stage[45]. Many of the trials admitted women in various stages of the menopausal transition, thus making it difficult to determine treatment effects in different menopausal transition stages characterized by different endogenous estrogen levels.

The use of isoflavones for symptom management also requires evaluation of risk. Some examples of the adverse events of the trials included gastrointestinal symptoms, bloating, constipation, nausea, headaches, cystitis, back pain, and systemic rash. For more detailed information pertaining to each specific study, see Table 3.

Another challenge of this review was the difficulty of comparing results from use of many different scales, as detailed in Appendix 1. Often, only total scores were given making it difficult to determine what specific symptoms were affected.

Conclusion

In summary, this systematic review of soy isoflavones, other isoflavones, isoflavone combinations, and amino acids suggest the most promising area for future study is in the other isoflavone category and the isoflavone combinations category. Most of the trials in the other isoflavones category showed an improvement in hot flashes and showed some evidence for significant reduction in multiple co-occurring symptoms. Soy isoflavone trials were much less effective and amino acid trials revealed no treatment effects on any of the symptoms.

These trials indicate that further research is warranted, especially on other isoflavones and isoflavone combinations. In particular, importance must be placed on adherence to the

CONSORT criteria so that these trials can be held in high regard by practicing clinicians who are seeking alternatives to hormone therapy for symptomatic women who are in the early or late menopausal transition or women who are post menopausal.

For example, increasing the sample size and reporting complete control data will increase the accuracy of statistical analyses. Also, reporting the composition of isoflavones (genistein, diadzein, and glycitein) will help to determine which isoflavone and its dosage is the most beneficial for the relief of menopausal transition symptoms. In relation to this, separating women into groups of equol producers vs. non-equol producers is crucial to determine whether or not isoflavones relieve the symptoms of women who do not produce equol. Inclusion criteria, such as specific levels of frequency or severity of symptoms studied, must be considered in order to test those specific symptoms (e.g., hot flash frequency and severity). Finally, reporting subscales and not only total scale scores will enable researchers to determine which specific symptoms were significantly or not significantly reduced.

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Appendix 1. Measurement Subscales and Symptoms Defined as Appropriate Measures for Each Symptom Group of Interest

Scales, Subscales and Symptoms Used	Vasomotor Symptoms	Mood Disturbances	Sleep Disturbances	Pain Symptoms	C
Greene Climacteric Scale[32] Subscale Name Symptoms accepted	Vasomotor (2) hot flashes, night sweats	Depressed Mood 5) depressed, crying spells, irritability	NA (combined with mood & cognitive)	Somatic (7) headache, muscle/joint pain	N r
Kupperman Index[33] Total scale Symptoms accepted	Cannot use total vasomotor	Cannot use total melancholia	Cannot use total insomnia	Cannot use total arthralgia/ myalgia, headache	N
Menopause Rating Scale[34]	NA (combined with sleep and pain	NA (combined with cognition)	NA (combined with HFs and pain)	NA (combined with HFs and sleep)	N r
Menopause Symptom Scale for Japanese women[35] * Total scale Subscale name Symptoms accepted	Cannot use total Vasomotor hot flashes	Cannot use total Psychological depression	NA (combined with anxiety)	Cannot use total Somatic headache backache	C C
Menopause-Related Quality of Life[36-37] Total scale Subscale name Symptoms accepted	Vasomotor hot flashes	NA (combined with cognition)	NA (combined with pain)	NA (combined with sleep)	N r
Simplified Menopausal Index[38]					N
Symptoms accepted	hot flashes	depression irritability melancholia	insomnia difficulty sleeping	joint pain headache arthralgia	
Pittsburgh Sleep Quality Index[39]	NA	NA	PSQIDISTB awakening at night	NA	N

Scales, Subscales and Symptoms Used	Vasomotor Symptoms	Mood Disturbances	Sleep Disturbances	Pain Symptoms	C
Subscale name Symptoms accepted					
Profile of Mood States[40-42] Subscale name Symptoms accepted	NA	Anger-Hostility grouchy/irritable Fatigue-Inertia anxious	NA	NA	N
Identical Pictures Test[43] Symptoms tested	NA	NA	NA	NA	p c
Verbal Fluency Test[43] Symptoms accepted	NA	NA	NA	NA	p p
Trail Making Test[44] Symptoms accepted	NA	NA	NA	NA	p p

Note: NA = not applicable, e.g. no subscale appropriately matching symptom group; NM = not measured; (#) number of symptoms in subscale.

Note: Where scale or subscale and symptoms are noted, the symptoms listed met our criteria as indicators of the symptom groups in the review.

Names of subscales and symptoms are those used in the scale.

(#) total number of symptoms in the measured scale or subscale

* grouped according to the Greene Climacteric Scale

** not reported

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Table 1

Trial of Isoflavones and Amino Acids for Hot Flashes and Co-occurring Symptoms: Study Population, Design, Interventions, Outcome Measures and Results

Author, Year, Study Location	Study Population, Sample Size (screened, enrolled, completed, followed)	Study Design	Main Intervention & Comparison/ Control	Outcome Measure: Hot Flashes	Outcome Measure: Other symptoms	Results: Hot Flashes	Results: Co-occurring symptoms
Soy Isoflavones							
Basaria[15], 2009, Maryland, USA	PM healthy women 46-76y, Tertiary care center, Caucasions 80% Black 10% Other 10% 93 randomized, 7 withdrew, 84 completed	Double blind RCT, 2 groups 12 weeks	Intervention: 20g soy proteinpowder in beverages x1qD 160mg total isoflavones: Genistein-64mg Diadzein-63mg Glycitein-34mg Control: Placebo powder in beverages x1qD (20g whole milk protein)	MENQOL Chi2 and ANOVA 2 sample ttest Wilcoxon sum rank test Linear Regression	MENQOL Chi2 and ANOVA 2 sample ttest Wilcoxon sum rank test Linear Regression Cognition tests: NART Rotating cubes, Identical pictures, Verbal fluency, Trail making A, Trail making B, GPTcDH, GPT c NDH, Grooved Pegboard=	B-group: Vasomotor (no subscale breakdown): Baseline= NS 6 wks= NS 12 wks= NS	B-group: Psychosocial (NA): Baseline= NS 6 wks= NS 12 wks= NS Physical (NA): Baseline=* 6wks=NS 12nwks=NS COGNITION All NS Soy=*** COGNITION All NS (NA)
					GPT Dominant Hand= DH		
Hanachi[16], 2008, Iran	PM women 51.3y (4.6) BMI 26.6 (3.9) Ethnicity NR Screened=NR Enrolled=37 Completed=NR Lost to f/ u=NR	RCT, 12 weeks	Intervention: 12.5g soy protein in soy milk per day Genistein-13mg Diadzein-4.13mg Comparison: Soymilk + Exercise (1 hour of walking/D) Control specifics =NR	KI: Percent decrease in symptoms	KI: Percent decrease in symptoms: Depression, Insomnia, Forgetful, Muscle/Joint pains	B-group or W-group?: Soymilk=72% ↓* Soymilk + Exercise=83% ↓* Control group=NR % change “after soymilk”	B-group: MOOD (Depression) Soymilk only 58% ↓ NS Soymilk +Exercise= 18% ↓ NS SLEEP (Insomnia) Soymilk only 35% ↓ NS Soymilk+Exercise, 28% ↓ NS COGNITION (Forgetful) Soymilk only 55% ↓ NS Soymilk+Exercise, 20% ↓ NS PAIN (Muscle/Joint) Soymilk only, 33% ↓ NS Soymilk+Exercise, 30% ↓ NS
							Control groups: NR
Jou[17], 2008, Taiwan	Healthy, menopausal women, University Hospital Clinics 49.8- 57.6y BMI= 19.8- 26 kg/m2	Double blind RCT 6 months	Intervention: 3g soy germ extract powder 2x qD= 6g total soy	KI, Linear Mixed Model Approach	KI subscores	B-group: 3 months EP * Non-EP NS Control βo NS 6 months EP*	B-group: 3 & 6 months: Sleep (Insomnia) =NS Mood (Melancholia)= NS Pain (Headaches) =NS

Author, Year, Study Location	Study Population, Sample Size (screened, enrolled, completed, followed)	Study Design	Main Intervention & Comparison/ Control	Outcome Measure: Hot Flashes	Outcome Measure: Other symptoms	Results: Hot Flashes	Results: Co-occurring symptoms
	120 screened 96 randomized 7 lost to follow-up 89 completed 120 screened 96 randomized 7 lost to follow-up 89 completed 120 screened 96 randomized 7 lost to follow-up 89 completed		protein, 135mg isoflavones qD Genistein-17.1mg Diadzein-65.4mg Gycitein-52.5mg Control: Roasted wheat powder			Non-EP NS Control βo NS EP= Equol Producing Non-EP= Non Equol Producing	
Welty[18], 2007, Boston, MA USA	PM + MT women <4.5 HF/d 51.9y (5.5) BMI=27.9 (5.5) >4.5HF/d 54.6y (5.4) BMI=23.9 (4.0)	RCT crossover design 4 wk TLC diet, then 8 wks, then crossover 8wks = 16 weeks total	Intervention: 25g soy protein in soy nuts (aka roasted soy beans, unsalted, ½ cup qD) Genistein-61mg Diadzein-30mg Glycitein-10mg (=101mg isoflavones) Comparison: TLC diet aka	Outcome measure HFs: Daily diary MENQOL Urine Isoflavone HPLC	Outcome measure (Other): MENQOL	Results HFs: B-group: MENQOL scores Soy nut grp: Vms (no breakdown-NA): 19% ↓ *** C: no change in scores W + B group (HFs): Daily diary: C: 22.3(23.5) to 23.3(23.5) HFs/wk [No decrease]	Results (Other): B-group: MENQOL scores Soy nut grp: Psychsocial (NA): 12.9% ↓ ** Physical (NA): 9.7% ↓*
	197 screened 82 enrolled 22 dropped out 60 completed 39/60 had HFs		Therapeutic Lifefstyle Change diet, recommended by Nat'l Cholesterol Ed. Program 30% energy from total fat, 15% protein, 55% carbs, 1200mg Calcium, 2 fatty fish meals q week.			>4.5HF grp: 45% ↓ 7.5(3.6) to 4.1(2.6) *** <=4.5HF grp: 41% ↓ 2.2(1.2) to 1.3(1.1) *** HF reduction in soy grps noticeable at 2 weeks (53% ↓ in >4.5HF grp and 54% ↓ in <=4.5HF grp)	
Lewis[19], 2006, Canada	PM women 45-60y Age: S 53.3(3.1) C 52.9(3.6) F 53.2(2.9) 792 women screened 99 randomized 87 completed	RCT Double blind Intention to tx 3 arm parallel 16 wks	Soy flour muffins (25g soy) Isoflavones 42mg total: Genistein 25.7mg Diadzein 15.5mg Glycitin 0.7mg Comparison: Ground flaxseed (25mg) muffins(F):	MENQOL Hot flash diary	MENQOL Only Vsm + Psych/Social breakdown Vsm= vasomotor	B-group: MENQOL: Vsm (NA) (S, C, F) NS HF diary: Severity (S, C, F) NS Frequency (S, C, F) NS Vsm (NA) (S, C, F) NS	B-group: MENQOL Psych/Social (NA): NS
	S=Soy C=Control F=Flaxseed Some women were taking Black Cohosh during the study.		50mg/d of secoisolariciresinol diglycoside. Wheat flour (C) muffins (all isocaloric)				
Other Isoflavones							

Author, Year, Study Location	Study Population, Sample Size (screened, enrolled, completed, followed)	Study Design	Main Intervention & Comparison/ Control	Outcome Measure: Hot Flashes	Outcome Measure: Other symptoms	Results: Hot Flashes	Results: Co-occurring symptoms
Evans[20], 2011, Canada	PM women (3 were "peri"-menopausal women Genistein: 53.39y (5.05) BMI 25.5 (3.8) C: 53.50y (4.44) BMI 26.4 (3.8) Ethnicity NR 163 screened 84 enrolled 82 completed 3 lost to f/u	RCT Double blind 12 weeks	Intervention: Synthetic Genistein 30mg capsule 1qD Control: Placebo capsule Microcrystalline Cellulose 1 qD	GCS Daily diary	GCS	(Intention to tx data) B-group: HF/d: G: 9.1 to 4.7** 51.2%↓ C: 10 to 7.2 Duration (min) of HF: G: 23.63(17.70) to 11.86(11.82)** vs. C: 37.95(48.42) to 22.65(22.47) Avg severity: NS Scale 0-3 G: 1.86(0.43) to 1.70(0.58) vs C: 2.06(0.39) to 1.96(0.57) (Per protocol analysis) HF/d: G: 9.8 to 4.8* 51.2% ↓vs. C: 9.9 to 7.1 29.8% ↓ GCS Vsm (NA-no breakdown) NS	GCS: B-group: MOOD: Depression NS
Carmignani[21], 2010, Brazil	Healthy, symptomatic c PM women 52.4y(3.9) BMI: HT 25.9 Soy 26.4 C 26.6 HT-65% white, 35% non white Soy-40% white! 60% non white C: 70% white, 30% non white 1520 screened, 60 enrolled, 60 completed, none lost to f/u	Double blind, RCT 3 groups 16 weeks	Intervention: 90 mg total isoflavone powder mixed c water: diadzein 16 mg genistein 30mg glycitein 7 mg 1 placebo tab qD+ soy powder 2x qD (45mg isoflavones each dose) HT: 1mg estradiol 0.5mg norethisterone Placebo powder: 40 g maltodextrin 1 tab per day+ placebo powder 2x qD Placebo: 1 placebo tab qD+ placebo powder 2xqD	MRS with some subscale breakdown	MRS with some subscale breakdown	B-group: Somatic subscale: (HFs) HT-Soy=NS HT-C=** Soy-C=*	B-group: Somatic subscale: PAIN (Joint/musc): HT-Soy=NS HT-C=** Soy-C=* SLEEP (Sleep problems-NA)=NS Psych subscale: MOOD (Depression)=NS (Irritability)=NS (Anxiety)=NS

Author, Year, Study Location	Study Population, Sample Size (screened, enrolled, completed, followed)	Study Design	Main Intervention & Comparison/ Control	Outcome Measure: Hot Flashes	Outcome Measure: Other symptoms	Results: Hot Flashes	Results: Co-occurring symptoms
Lee[22], 2010, Korea	45-60y PM >6 mos amenorrhea BMI>30 kg/m2	Double blind RCT 2 groups 12 wks Universit	Intervention; Rexflavone: Sophorae fructus extract 20% isoflavones Capsule=175mg	KI	KI	B-groups: Rex-C= NS (0.0542) KI >20: * (12 weeks) KI 8 weeks *	B-groups: SLEEP Insomnia=NS MOOD Melancholia=NS PAIN
	117 recruited, 87 assigned. Rexflavone 43-(4 dropouts) = 39 -4 no complete=3 5. Placebo 44-(3 dropouts)= 41-10 no complete=3 1. 66 completed the study.	y hospital/clinic	Rexflavone Dose=1cap 2xD Control: Placebo capsule=400mg vehicles such as altodextrin, magnesium stearate and microcrystalline cellulose				Joint/pain=NS HA=NS Total KI score=*
Albertazzi[23], 2005, Italy & UK	PM women 44-65y (x=54y) G 53y(3) C 54y(3) BMI G 26(3) C 28(8) All Caucasian 178 screened 121 enrolled 100	RCT Crossove r study Blinded (researchers) 6wks + 6 wks 12 wks total	Intervention: Genistein 90mg 1 capsule qD Placebo: 1 capsule qD	GCS Hot Flush diary Wilcoxon signed rank test Random coeficient's regression model	GCS	B-group: Hot flush score Subgroup flush score >=9 G: * C: NS GCS (Vsm-> NA)	B-group: From GCS: MOOD Anxiety NS Depression NS C: NR (“Compared to placebo”)
	randomized 99 completed						
Hildago[24], 2005, Ecuador	PM women 51.3y (3.5) BMI 26.6 (3.9) Screened NR 60 enrolled 53 completed	RCT Double blind Crossove r c 7 day washout 12 wks + 12 wks = 24 wks total	Intervention: Commercially available red clover (RC) isoflavone supplement 80mg/d total 2 capsules qD (40mg each Control: Placebo capsule 2 qD	KI % ↓ in sxs	KI % ↓ in sxs	B-group: HFs * Night sweats * C: NS	B-group: SLEEP (NA) Sleeping disorders* MOOD (Dep)* COGNITION (lack of concentration)* PAIN (Arthralgia)* (Headache)*
Jou[25], 2005 Taiwan/UK	Women undergoing MT Age NR BMI NR Ethnicity NR 48 recruited Screened NR Randomized NR Completed NR	Randomized trial Single center Prospective	Intervention: Isolflavone 70mg 4 Capsules 325mg containing 17.5mg isoflavones per capsule Comparison: Isoflavone 35mg 2 Capsules 325mg containing 17.5 mg of	GCS scores Wilcoxon signed rank test	GCS scores Wilcoxon signed rank test	B-group: Vsm (NA) 70mg group* (Compared to 35mg group=C)	B-group: Compare to 35mg group = Control MOOD 35mg (12 weeks): Psychological: Anxiety* Depression* 70mg(12 weeks): Pscyhological: Anxiety*

Author, Year, Study Location	Study Population, Sample Size (screened, enrolled, completed, followed)	Study Design	Main Intervention & Comparison/ Control	Outcome Measure: Hot Flashes	Outcome Measure: Other symptoms	Results: Hot Flashes	Results: Co-occurring symptoms
			isoflavones per capsule. isoflavones per capsule.				Depression NS (Not used d/t control & tx both significant)+
Uesugi[26], 2004 Japan	Climacteric Japanese women Age 58y(7) 44-74y BMI 23.0(3.7) 58 volunteer participants Screened NR	RCT Double blind Crossove r study 2 4-wk periods 8 weeks total	Intervention: Isoflavone (IF) 40mg tablet Daidzein 3.41mg Genistein 0.91mg Glycitein 2.70 mg Control: Placebo tablet (Contents not described)	Questionnaire Interview SMI (Simplified Menopausal Index)	Questionnaire Interview SMI (Simplified Menopausal Index)	B-group: For SMI>26 IF vs. placebo * EQUOL: no HF data	B-group: All other sxs NS Compared to placebo SLEEP Insomnia NS MOOD Depression NS PAIN Joint pain NS EQUOL: no sx data
Combinatio ns							
Ishiwata[27], 2009, Japan	Symptomatic Japanese women 39 Pre-25 Peri-70 PM 40-59y C: 50.6y (4.9) BMI 22.3(3.0) EQ-1: 50.5y (4.7) BMI	RCT Double blind 12 wks	Interventions: EQ-1: 10mg equol per day EQ—3: 30mg equol per day 1 supplement packet contained: S-equol 10mg Daidzein 0.8mg Genistein 2 mg Glycitein 4.5mg Placebo= C	Menopausal sx Scale for Japanese women questionnaire Daily diaries GCS	Profile of Mood States (POMS) questionnaire 24h urine samples Menopause sx Scale for Japanese women ~GCS	B-group: *EP* Menopause Scale: Vasomotor (NA) *Non-EP* Vasomotor (NA) EQ-3 NS C * EQ-1 NS EQ-3 *	B-group: *EP* Menopause Scale: MOOD (Depression) NS POMS (NA) *Non-EP* Menopause Scale: MOOD (Depression) NS POMS: Fatigue-Inertia *anxiety EQ-3
	22.3(3.0) EQ-3: 50.5Y (4.7) BMI 22.0 (3.0) 141 screened 134 randomized 127 completed		Supplement packet containing lactose				*Non-EP* Meno scale: MOOD (Depression) NS POMS: MOOD Anger-Hostility NS Fatigue-Inertia NS
Mucci[28], 2006, Italy	Symptomatic menopausal women 53.8y ES: 53.3y(5.6) Ca+D: 54.4y(6.1) BMI,ES: 25.2(3.5) BMI, Ca+D: 23.2(3.3) Ethnicity NR 89 women 44 ES, 45 Ca+D Screened NR Enrolled NR	RCT Multi-center Longitudi nal, parallel groups 24 wks	Interventions: Magnolia Bark Extract (ES) 60mg and Magnesium 50 mg Isoflavones 60mg: (Genistin 30mg Diadzin 30mg) Lactobacillus 500 million spores Calcium 141 mg Vitamin D3 5µg 1 tab qD of ES Comparison: Calcium 141mg Vit D3 5µg	Chi square Fisher's exact test ANOVA Change vs Baseline % Absence of Sxs (Disappearan ce rate)	Chi square Fisher's exact test ANOVA Change vs Baseline % Absence of Sxs (Disappearance rate)	B-group: Wk 2 ** Wk 12 ***	B-group: SLEEP (Insomnia): Wk 2** Wk 12*** MOOD (Irritability, anxiety, depression) Wk 2** Wk 12***

Author, Year, Study Location	Study Population, Sample Size (screened, enrolled, completed, followed)	Study Design	Main Intervention & Comparison/ Control	Outcome Measure: Hot Flashes	Outcome Measure: Other symptoms	Results: Hot Flashes	Results: Co-occurring symptoms
			1tab qD of Ca+D				
Secreto[29], 2004, Italy	PM women Iso+Meloto nin: 53y(50-57) BMI 23.8 (21.5-26.8) Iso alone: 52y (49-54) BMI 25.0 (22.8-26.0) Melatonin alone: 52y (50-57) BMI 23.6 (21.8-26.8) Control: 52y (50-55) BMI 24.0 (21.9-26.8) 388 screened 262 randomized 232 analyzed 9 lost to f/u	RCT Double blind Multicen ter 2×2 factorial 12 weeks	Interventions: Isoflavones: Diadzein 40mg Glycitein 28mg Genistein 12mg Grp1: Soy isoflavones (80mg)+melatonin (3mg) Grp2: Soy Isoflavones(80mg) + placebo melatonin Grp3: Placebo soy Isoflavones+ melatonin (3mg) Grp4: Placebo soy+ placebo melatonin Placebo=excipient only, sorbitol.	GCS (Only 2 items for HFs questioned by the authors)	GCS	B-group: Vasomotor (NA): Isoflavones alone larger % dec in sxs: Iso 74.6% ↓ NS C 69% ↓ Mel 61.1% ↓ NS Iso+Mel 62.3%↓ No statistical data due to high placebo score. Avg GCS vasomotor baseline=4 Some members (22) had a “zero” score for vasomotor sxs and were not equally distributed among the groups No subscale breakdown	B-group: MOOD (Psych-NA): Iso +Mel: ↑ improvement than others NS No improvement: Iso+mel 18% Iso 29% Mel 30% C 29% No statistical data due to high placebo score. No subscale breakdown
Amino Acids							
Guttoso[30], 2009, New York	PM women Mean age 54.5/54.1;	Double blind; 2 grps;	Intervention: methionine 2 gm/day (Grp A)	Daily HF diary; 1° outcome	Questionnaire at baseline to wk 12 &	B-group: HF composite & HF Baseline Score = NS	B-group: SLEEP (quality): (PSQI-global) NS
	White (96%/81%) Volunteers TV & newspaper ads; used FSH to dx menopause; all hf; no BSO; hyst (16%/15%); no HRT; 378 screened; 51 randomized into 2 grps; 47 completed	randomized (25/26); concealed; baseline to 12 wks (Phase 1)	Control: placebo (Grp B) Placebo= Cornstarch + microcellulose	measure % chg in HF composite score (severity + freq); 2° outcome measure included % chg HF freq; baseline to 12 wks & baseline to 20 wks Also HFBS (1-10); high=extreme bother	baseline to wk 20 PSQI global score 0-21; high=worse	Grp B 33.4% ↓ Baseline thru 12 wks	(NA)
Guttoso[31], 2008, New York	PM Mean age 56.1/55.7; White (92%/96%) Volunteers TV & newspaper ads; used FSH to dx menopause; all hf; hyst	2grps (50/50); randomized; concealed; baseline to 12 wks (Phase 1)	Intervention: l-isoleucine 5 mg/day (Grp A) Control: placebo (Grp B) placebo contents not described	Daily HF diary: daily for 1 wk baseline, 1 wk during wks 1-4, 1 wk during wks 8-12, 1 wk during wks	Ques at baseline, wk 12 & wk 22 PSQI global score 0-21; high=worse	B-group: Hf freq & hf composite & PPHFS -all NS	B-group: SLEEP (quality) (PSQI-global) NS (NA)

Author, Year, Study Location	Study Population, Sample Size (screened, enrolled, completed, followed)	Study Design	Main Intervention & Comparison/ Control	Outcome Measure: Hot Flashes	Outcome Measure: Other symptoms	Results: Hot Flashes	Results: Co-occurring symptoms
				16-17 & 1 wk during wks 21-22; hf sev 16-17 & 1 wk during wks 21-22; hf sev 16-17 & 1 wk during wks 21-22; hf sev			
	(30%/36%); no HRT; Phase 1: 100 randomized into 2 grps; 86 completed			recorded when occurred; Also PPHFS			

Key: B-group = Between groups

C = control

EP = Equol producing

GCS = Greene Climacteric Scale

HF = Hot flash

HT = Hormone therapy

KI = Kupperman Index

MENQOL = Menopause Quality of Life Scale

MRS = Menopause Rating Scale

MT = Menopausal transition

Non-EP = Non equol producing

NA = Not applicable

NR = Not reported

NS = Not significant

POMS = Profile of Mood States

PPHFS = Patient Perceived Hot Flash Score

PM = Post menopausal

PSQI = Pittsburgh Sleep Quality Index

VMS = Vasomotor symptoms

Table 2

Summary of Treatment Outcomes (Between-Group Differences) for Hot Flashes and Co-occuring Symptoms for Isoflavones and Amino Acids.

Study/Type of Intervention	Hot Flashes	Mood Disturbances	Sleep Disturbances	Pain Symptoms	Cognitive Disturbances
Soy Isoflavones					
Basaria[15] 2009 Soy protein 20 g vs. Whole milk protein 20 g	NA	NA	NA	NA	NS
Hanachi[16] 2008 Soy protein 12.5 g in soy milk vs. Soymilk + walking 1 h	?	NS	NS	NS	NS
Jou [17] 2008 Soy germ extract 6 g vs. Roasted wheat	+ (EP women)	NS	NS	NS	NM
Welty[18] 2007 Soy protein (soy nuts) 25 g vs. TLC (Lifestyle Change) diet	+	NA	NA	NA	NA
Lewis[19] 2006 Soy 25 g in soy flour muffins vs. ground flaxseed muffins vs. wheat flour muffins	NS	NA	NA	NA	NA
Other Isoflavones					
Evans[20] 2011 Synthetic genistein 30mg vs. placebo	+	NS	NA	NA	NA
Carmignani[21] 2010 Isoflavone powder 90 mg vs. HT vs. placebo	+	NS	NS	+	NA
Lee[22] 2010 Rexflavone 350mg vs. placebo (BMI>30)	+ (KI>20)	NS	NS	NS	NM
Albertazzi[23] 2005 Genistein 90mg vs. placebo	+ (For GCS>9)	NA	NA	NA	NA
Hildago[24] 2005 Red clover isoflavone 80mg vs. placebo	+	+	NA	+	+
Jou[25] 2005 Isoflavone 70 mg vs. Isoflavone 35mg	NA	NS	NA	NA	NA
Uesugi[26] 2004 Isoflavone 40 mg vs. placebo	+ (SMI>26)	NS	NS	NS	NM
Isoflavone Combinations					
Ishiwata[27] 2009 10mg EQUOL vs. 30 mg EQUOL vs. placebo (EP vs. Non-EP)	NA	+ (Non-EP, 30 mg)	NA	NA	NA
Mucci[28] 2006 Magnolia bark extract 60 mg +Magnesium 50 mg +Isoflavone 60 mg+	+	+	+	NM	NM

Study/Type of Intervention	Hot Flashes	Mood Disturbances	Sleep Disturbances	Pain Symptoms	Cognitive Disturbances
Calcium+Vit D vs Calcium + Vitamin D					
Secreto[29] 2004 Isoflavone 80 mg +Melatonin 3 mg vs. Melatonin vs. placebo	NA	NA	NA	NA	NA
Amino Acids					
Guttoso[30] 2009 Methionine 2g vs. placebo	NS	NM	NA	NM	NM
Guttoso[31] 2008 L-Isoleucine 5mg vs. placebo	NS	NM	NA	NM	NM

NS = Not significant;

NM = Not measured;

NR = Not reported;

NA = Not applicable;

+ = Significant @ $P \leq .05$.;

EP = Equol Producing Women;

SMI = Simplified Menopausal Index

Table 3

Adverse Events from the Trials of Soy Isoflavones, Other Isoflavones, Isoflavone Combinations, and Amino Acids

Study/Type of Intervention	Side effect/Adverse events
Soy Isoflavones	
Basaria[15] 2009 Soy protein 20 Gm vs. Whole milk protein 20 Gm	Gastrointestinal upset, bad taste
Hanachi[16] 2008 Soy protein 12.5 Gm in soy milk vs. Soymilk + walking 1 h	Not reported.
Jou [17] 2008 Soy germ extract 6 Gm vs. Roasted wheat	Not reported.
Welty[18] 2007 Soy protein (soy nuts) 25 mg vs. TLC (Lifestyle Change) diet	Flatulence, bloating, constipation, weight gain.
Lewis[19] 2006 Soy 25 mg in soy flour muffins vs. ground flaxseed muffins vs. wheat flour muffins	Generalized aching, gastrointestinal symptoms
Other Isoflavones	
Evans[20] 2011 Synthetic genistein 30mg vs. placebo	Breast tenderness, cramps, increase in hot flashes, spotting, bloating, nausea, recurrent headaches, frequent urination, & body itching reported in both placebo & treatment groups; no significant differences between groups.
Carmignani[21] 2010 Isoflavone powder 90 mg vs. HT vs. placebo	Mastalgia, vaginal bleeding, skin problem-allergy, headache, nausea, weight gain, water retention, & intestinal complaints; no significant differences between groups.
Lee[22] 2010	Mild to moderate cases of lumbago, cutaneous
Rexflavone 350mg vs. placebo (BMI>30)	lesions in placebo group; Mild to moderate cases of cystitis in treatment group.
Albertazzi[23] 2005 Genistein 90mg vs. placebo	Bloatedness and back pain in treatment group.
Hildago[24] 2005 Red clover isoflavone 80mg vs. placebo	Headache reported for one placebo and one treatment group.
Jou[25] 2005 Isoflavone 70 mg vs. Isoflavone 35mg	Headache, breast tenderness, edema, dizziness, anorexia, and fatigue reported for both groups; No significant differences between groups.
Uesugi[26] 2004 Isoflavone 40 mg vs. placebo	“Safety confirmed by stable liver functional markers and immunologic markers” p. 227.
Isoflavone Combinations	
Ishiwata[27] 2009 10mg EQUOL vs. 30 mg EQUOL vs. placebo (EP vs. Non-EP)	Systemic rash in one EQ-3 woman; no other adverse events reported.
Mucci[28] 2006 Magnolia bark extract 60 mg+Magnesium 50 mg+Isoflavone 60 mg+ Calcium+Vit D vs Calcium + Vitamin D	Gastic discomfort in one ES participant at day 30 lasting one day without requiring any action.
Secreto[29] 2004 Isoflavone 80 mg+Melatonin 3 mg vs. Melatonin vs. placebo	Gastric intolerance, tachycardia, Increased body weight, insomnia, excessive drowsiness, headache, and constipation were equally reported among all groups.
Amino Acids	
Guttoso[30] 2009 Methionine 2g vs. placebo	Nausea, worsening hot flashes, induced elevation in serum homocysteine.
Guttoso[31] 2008 L-Isoleucine 5mg vs. placebo	Nausea, hand edema, herpes zoster, edema, arthralgias, myalgias, stroke, and infection.