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The effect of soy protein containing soy isoflavones on serum concentration of cell adhesion molecules: A systematic review and meta-analysis of randomized controlled trials

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ABSTRACT

Background: Soy protein in combination with soy isoflavones might reduce the serum concentration of inflammatory mediators. In this study, we attempted to summarize the effect of soy protein combined with soy isoflavones on circulating E-selectin, intercellular adhesion molecule-1 (ICAM-1), and vascular cell adhesion molecule-1 (VCAM-1) in adults.

Methods: Clinicaltrials.gov, Web of Science, Cochrane Library, PubMed, and Scopus were searched for English articles with no time limit regarding publication up to December 2020. Thereafter, the mean changes from baseline and their standard deviations (SDs) for both intervention and comparison groups were used to calculate the effect size. We used DerSimonian and Laird random-effects model if the heterogeneity test was statistically significant. Cochran's Q test and I-squared statistic were also used to calculate the statistical heterogeneity of the intervention effects.

Results: Eight articles were found as eligible for this study. The treatment duration was between 6 and 24 weeks. Soy isoflavones dose was in a range of 30–112 mg/day and soy protein dose was in a range of 11.25–52 g/day. Overall, taking soy protein supplements containing soy isoflavones was not associated with changes in cell adhesion molecules, E-selectin, ICAM-1, or VCAM-1 (WMD = 0.65, 95 % CI: -2.58, 3.89; p = 0.692; WMD = 2.68, 95 % CI: -0.98, 6.34; p = 0.151; WMD = 2.66, 95 % CI: -6.28, 11.61; p = 0.559, respectively).

Conclusion: The combination of soy protein and soy isoflavones was not significantly associated with changes in levels of E-selectin, ICAM-1, and VCAM-1. However, we need more studies with a large sample size and more participants with different age categories in this regard.

1. Introduction

Chronic inflammation known as the most important risk factor for cardiovascular diseases (CVDs) [1] which is responsible for nearly 30 % of all deaths in low-and middle-income countries. [2–4] Inflammation can modify both the morphology and function of endothelial cells, persistently activate endothelial cells, and contribute into endothelial dysfunction. [5] Furthermore, cytokine enhancement causes the expression of glycoproteins gene of endothelial cells such as E-selectin, intercellular adhesion molecule-1 (ICAM-1), and vascular cell adhesion molecule-1 (VCAM-1). [6] Under normal conditions, cell adhesion molecules (CAMs) are associated with cell-matrix adhesion and cell-cell communication, so these molecules can control the locomotion and migration of leukocytes across the endothelium. However, under some abnormal conditions like hypertension, the increased CAMs level can result in accelerating the progression of atherosclerosis. [7]

The concentration of inflammatory mediators could be affected by various factors such as diet and specific nutrients. [8,9] The diet's effects on endothelial function and serum levels of inflammatory mediators have been examined in some previous studies. [10,11]

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Since soy peptides may have anti-inflammatory effects, [12] some articles have investigated the effects resulted from the soy consumption. [13,14] According to the results of these studies, the reduction in animal protein intake and the increase in soy protein intake might consequently decrease the serum concentration of CAMs and other inflammatory mediators. [13,14] Soy contains a high amount of L-arginine and previous experimental studies have indicated that L-arginine supplementation could decrease the expression of inflammatory cytokines. [15] Moreover, in vitro studies have proposed that L-arginine as nitrite oxide (NO) donors can prevent the expression of pro-inflammatory genes by the inhibition of nuclear factor kappa B (NFκB). [16,17]

Besides protein, soy also contains phytoestrogens, which are individually associated with the reduced levels of inflammatory mediators and improved endothelial function. Soy isoflavones are bioactive molecules with a similar structure to 17b-estradiol. [18] Soy isoflavones have been hypothesized to have the ability of protection against coronary vascular disease by increasing nitric oxide and reducing CAMs concentrations. [19–27]

Moreover, scientists have proposed that soy isoflavones can modulate the expression of inflammatory genes by inhibiting the c-Jun N-terminal kinase (JNK) pathway as well as regulating the pathways involved in both the peroxisome proliferator-activated receptor alpha (PPAR-α) and –γ activation. [28,29]

However, the results of previous randomized clinical trials (RCTs) are contradictory in this regard. Some studies indicated the beneficial effects of soy products on concentrations of CAMs, while some other studies reported no effect. Therefore, since there was no study assessing the effect of soy protein containing isoflavones on E-selectin, ICAM-1, and VCAM-1 on adults, in the current study, we attempted to conduct a systematic review and meta-analysis to summarize the effect of soy protein containing isoflavones on CAMs among adults.

2. Materials and methods

We used PRISMA-2020 (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) checklist for all steps of the present systematic review and meta-analysis (Supplementary appendix).

Of note, a systematic search was performed using Clinicaltrials.gov, Web of Science, Cochrane Library, PubMed, and Scopus up to December 2020. Accordingly, the query syntax for searching these databases is reported in Table 1, in the supplementary appendix. In order to find more eligible articles, the reference list of all the selected articles was manually searched, as well. To design the search strategy, we used Boolean operators (AND & OR). In addition, to search the exact terms, we used quotation marks, and to search all words derived from one keyword, asterisks were used. It is noteworthy that if the database was searched based on the keywords of E-selectin, ICAM1 and VCAM1, few articles would be missed. To this end, some key words related to the most important inflammatory mediators were used. All the found articles were then imported to EndNote software (reference manager software, version X6) and two reviewers (MH and AGh) separately read their titles and abstracts. Any discrepancy at this stage was resolved by the group discussions. We did not limit our search to study design and publication time. The protocol of this study was registered with PROSPERO (No. CRD42020166053).

2.1. Inclusion criteria

Two reviewers (MH and AGh) decided on including or excluding articles from the current systematic review and meta-analysis in terms of the following criteria. The inclusion criteria for this systematic review and meta-analysis were the PICOS (Patient/Population, Intervention, Comparison, Outcome, Study types) framework as follows: I) population: Healthy and unhealthy participants; II) intervention: Natural or commercial soy products containing both protein and isoflavones; III) comparison: Control group; IV) outcome: Reporting the baseline and follow-up levels of the serum concentrations of E-selectin, ICAM-1, and VCAM-1 in the intervention group or the comparison group; and V) study design: Parallel or cross-over RCT.

2.2. Exclusion criteria

The articles that met the following criteria were not included in our systematic review and meta-analysis: 1) articles reporting data in figures; 2) those that had a treatment duration less than one week; 3) those articles with no comparison group; 4) those articles that did not report the dose of soy protein or isoflavones or reporting no information to estimate them; 5) those in which participants took other food supplements besides soy products; 6) those articles in which the participants only took soy isoflavones or soy protein; 7) the articles reporting no information on the serum concentration of the desired outcome at baseline or after intervention and gave no information to compute it; and 8) non-English articles.

2.3. Data extraction

In this study, two reviewers (MH and AGh) independently performed the study's screening, methodological quality assessment, validation, and selection. Afterward, the following data were extracted from the selected studies: the information on study design, publication year, the country in which the study was conducted, the first-author's name, total sample size, sample sizes of both intervention and comparison groups, anthropometric and demographic variables (including sex, age, Body Mass Index (BMI)), health status, the dose of soy protein and isoflavones, kind of placebo, intervention duration, and the serum concentrations of E-selectin, ICAM-1, and VCAM-1 before and after performing the intervention. At this stage, any discrepancy was resolved through consulting until reaching an agreement. All the units regarding E-selectin, ICAM-1, and VCAM-1 were then converted into a same unit (ng/mL). As well, the studies with more than one comparison or intervention group were considered as separated articles. Of note, an email was sent to the corresponding author to clarify any unclear information, if needed.

2.4. Quality assessment

To assess the quality of the included RCTs, Cochrane Collaboration's tool was used by the two independent reviewers (MH and AGH). [30] The following items were then used to assess the risk of bias in this study: I) conducting adequate sequence generation; II) conducting allocation concealment; III) blinding both participants and personnel; IV) blinding the outcome assessment; V) incomplete report of outcome data; and VI) selective reporting. Each item was then judged as "low risk of bias", "high risk of bias", or "unclear risk of bias" by the reviewers; therefore, each one of the included studies in this review was scored as "good" if it met at least three items of low risk of bias, "fair" if it met at least two items of low risk of bias, and "weak" if it met less than two items of low risk of bias.

2.5. Data synthesis and statistical analysis

At this stage, mean differences (MDs) and their standard deviations (SDs), which were used to conduct this meta-analysis, were calculated by subtracting baseline values from the post-intervention values in the included articles.

The effect size of the intervention and comparison groups was calculated by the mean change from baseline and their SD was estimated in terms of the Cochrane Handbook. In those studies that reported standard error (SE), SD was calculated by multiplying SE in the square root of the sample size. Based on the Hozo's method, the mean was estimated using the median or range reported in the included articles. [31] Thereafter, both Cochran's Q test and I-squared statistic were used to

Table 1
Randomized controlled trial studies included in the systematic review and meta-analysis.

Code Author (year) (country)	Subjects	Age and BMI (mean ± SD)	RCT	Intervention	Placebo	Duration (week)	Variables	Results
1.1 Acharjee, S [36] 2015 Israel	Healthy postmenopausal women without metabolic syndrome N = 49	Age: 54.6 ± 5.8 BMI: 24.6 ± 3.8	Randomized, controlled, cross-over trial	0.5 cups/day soy nuts (containing 25 g of soy protein and 101 mg of aglycone soy isoflavones)	Non soy protein	8	ICAM-1, VCAM-1	There were no significant changes in between groups analysis regarding both ICAM-1 and VCAM-1
1.2 Acharjee, S[36] 2015 Israel	Healthy postmenopausal women with metabolic syndrome N = 11	Age: 54.1 ± 6.5 BMI: 31.8 ± 4.6	Randomized, controlled, cross-over trial	0.5 cups/day soy nuts (containing 25 g of soy protein and 101 mg of aglycone soy isoflavones)	Non soy protein	8	ICAM-1, VCAM-1	ICAM-1 decreased significantly in intervention group. VCAM-1 did not change significantly
2.1 Azadbakht, L [37] 2007 Iran	Postmenopausal women with the metabolic syndrome N = 42	Age: 57 ± 1.94 BMI: 28 ± 1.29	Randomized cross-over clinical trial	30 g/day soy nut (containing 11.25 g/day protein with 84 mg/day isoflavones)	Red meat	8	ICAM-1, VCAM-1, E-selectin	E-Selectin decreased significantly in intervention group. ICAM-1 and VCAM-1 did not significantly change
2.2 Azadbakht, L [37] 2007 Iran	Postmenopausal women with the metabolic syndrome N = 42	Age: 57 ± 1.94 BMI: 28 ± 1.29	Randomized cross-over clinical trial	30 g/day soy protein diet (containing 15 g/day protein with 102 mg/day isoflavones)	Red meat	8	ICAM-1, VCAM-1, E-selectin	E-selectin, ICAM-1, and VCAM-1 did not significantly change
3.1 Dettmer, M [13] 2012 USA	Prehypertensive/ Stage 1 Hypertensive Individuals N = 44	Age: 29 (24−43) BMI: 27.1 (25.2, 29.0)	Randomized clinical trial	Soy beverage prepared from soy protein isolate (containing 18 g soy protein and 30 mg soy isoflavones)	cow's milk beverage	8	ICAM-1, VCAM-1, E-selectin	ICAM-1, VCAM-1, and E-selectin did not change significantly
3.2 Dettmer, M [13]2012 USA	Prehypertensive/ Stage 1 Hypertensive Individuals N = 45	Age: 29 (24−43)* BMI: 27.1 (25.2, 29.0)	Randomized clinical trial	Soy beverage prepared from whole soy bean (18 g soy protein and 90 mg soy isoflavones)	cow's milk beverage	8	ICAM-1, VCAM-1, E-selectin	ICAM-1, VCAM-1, and E-selectin did not change significantly
4 Greany, K. A [19] USA 2007	Postmenopausal women N = 34	Age: 57.7 ± 6.0 BMI: 25.0 ± 4.3	Randomized cross-over	26 ± 5 g protein containing 44 ± 8 mg isoflavones per day	Milk protein	6	ICAM-1, VCAM-1, E-selectin	ICAM-1, VCAM-1, and E-selectin did not change significantly
5.1 Liu, Z. M [20] 2013 China	Normotensive Postmenopausal women N = 33	Age: N/M BMI: N/M	Double-blind randomized, placebo-controlled trial	15 g soy protein and 100mg Soy isoflavones	Milk protein and isoflavones placebo	24	ICAM-1, VCAM-1, E-selectin	ICAM-1, VCAM-1, and E-selectin did not change significantly
5.2 Liu, Z. M[20] 2013 China	Prehypertensive and hypertensive Postmenopausal women N = 87	Age: N/M BMI: N/M	Double-blind randomized, placebo-controlled trial	15 g soy protein and 100mg Soy isoflavones	Milk protein and isoflavones placebo	24	ICAM-1, VCAM-1, E-selectin	ICAM-1, E-selectin decreased significantly. VCAM-1 did not change significantly
6 Törmälä, R [38] 2008 Finland	Healthy postmenopausal women using tibolone N = 36	Age: 57.7 ± 0.8 BMI: 24.6 ± 5.3	Randomized, placebo-controlled, cross-over	52 g/day of soy protein containing 63 mg of genistein, 43 mg of daidzein and 6 mg of glycitein, altogether 112 mg of isoflavones	Milk protein	8	ICAM-1 and VCAM-1	ICAM-1 and VCAM-1 did not change significantly
7.1 Rebholz, C. M[39] 2013 USA	Hypertensive individuals N = 102 F = 34 M = 68	Age: 48.2 ± 11.7 BMI:29.5 ± 3.8	Randomized, placebo-controlled, double-blind, three-phase cross-over trial	40 g of soybean protein supplement (supplied 89.3 mg/day isoflavones)	Complex carbohydrate supplements	8	ICAM-1, VCAM-1, E-selectin	ICAM-1, VCAM-1, and E-selectin did not change significantly.
7.2 Rebholz, C. M[39] 2013 USA	Hypertensive individuals N = 102 F = 34 M = 68	Age:48.2 ± 11.7 BMI:29.5 ± 3.8	Randomized, placebo-controlled, double-blind, three-phase cross-over trial	40 g of soybean protein supplement (supplied 89.3 mg/day isoflavones)	Milk protein	8	ICAM-1, VCAM-1, E-selectin	ICAM-1, VCAM-1, did not change significantly. E-selectin decreased significantly
8.1 West, S. G[40] 2005 USA	Healthy men N = 14	Age: 57.36 ± 1.43 BMI: 25.89 ± 0.86	Randomized, double-blind, cross-over trial	25 g/day soy protein and 90 mg/day soy isoflavones	Milk protein	6	VCAM-1	VCAM-1 did not significantly change
8.2 West, S. G[40] 2005 USA	Postmenopausal women with hormonotherapy N = 6	Age: 70.40 ± 4.05 BMI: 26.17 ± 1.31	Randomized, double-blind, cross-over trial	25 g/day soy protein and 90 mg/day soy isoflavones	Milk protein	6	VCAM-1	VCAM-1 did not significantly change
8.3 West, S. G[40] 2005 USA	Postmenopausal women without hormonotherapy N = 12	Age: 59.08 ± 1.54 BMI: 26.80 ± 0.93	Randomized, double-blind, cross-over trial	25 g/day soy protein and 90 mg/day soy isoflavones	Milk protein	6	VCAM-1	VCAM-1 did not significantly change

Abbreviation: ICAM-1: Intercellular Adhesion Molecule, VCAM-1: Vascular cell adhesion protein; BMI: Body Mass Index; N/M: Not mention; RCT: Randomized clinical trial.

* Mean (95 % confidence interval).

calculate the statistical heterogeneity of the intervention effects. If the heterogeneity test's result was statistically significant, we would then estimate the summary of the overall effect and its heterogeneity using DerSimonian and Laird random-effects model. [32] A p-value≤0.10 for Cochran's Q test and the I-squared statistic value ≥50 % indicated a statistically significant heterogeneity. [33]

The sources of heterogeneity were found by conducting subgroup analysis, including age; sex; intervention duration; study design; BMI; the doses of soy protein and soy isoflavones; health status; sample size; geographical region; quality assessment; publication year; and baseline levels of E-selectin, ICAM-1, and VCAM-1.Subsequently, we evaluated the publication bias using Begg's funnel plot, Begg's rank correlation, and Eggar's weighted regression test. [34,35] Sensitivity analysis was also used to evaluate the effect of each study on the overall effect size. The statistical significance level was set at 0.05 and 95 % confidence interval was presented for all the calculated effect sizes. All the statistical analyses in this study were performed using STATA version 15 (Stata Corp, College Station, TX, USA).

3. Results

3.1. Systematic review findings

By searching all the above-mentioned databases, 4387 articles were retrieved. After identifying and removing duplicate articles, 2955 articles remained for reading the titles and the abstracts. Thereafter, by reading the titles and the abstracts, 2833 articles were excluded. Finally, 122 articles remained for assessing their full text. Next, based on the inclusion and exclusion criteria, 114 studies were excluded due to the following reasons: three articles were excluded due to the administration of soy intake mixed with other dietary regimens; two studies were removed because they had no comparison groups; 106 studies were excluded because the serum concentrations of E-selectin, ICAM-1, and VCAM-1 were not measured in them; one study was removed because the participants only took soy protein; and two studies were removed because the participants only took soy isoflavones. (Fig. 1). Therefore, this systematic review and meta-analysis included eight studies [13,19,20,36–40] (Table 1).

According to the results of our systematic review, five included studies assessed the effect of soy protein combined with soy isoflavones on the serum concentration of E-selectin. [13,19,20,37,39] Three studies were conducted on postmenopausal women [37,19,20] and two studies were performed on both men and women. [13,39] Notably, the range of soy protein dose was from 11.25 g/day to 40 g/day and the range of soy isoflavones administration was from 30 mg/day to 102 mg/day. As well, four studies had more than one intervention group; therefore, we considered them as the separated articles [37,13,20,39] (Table 1).

The effect of soy protein containing soy isoflavones on ICAM-1 was assessed in seven studies included in this review. [13,19,20,36–39] Five studies were conducted on postmenopausal women [37,19,20,36,38] and two studies were performed on both male and female cases. [13,39] The range of soy protein dose was between 11.25 g/day and 52 g/day and the range of soy isoflavones administration was between 30 mg/day and 112 mg/day. Of note, five studies had more than one intervention group; therefore, we considered them as the separated articles [37,13,20,39,36](Table 1).

In regard to VCAM-1, eight studies assessed the effect of soy protein containing soy isoflavones on the serum concentration of VCAM-1.

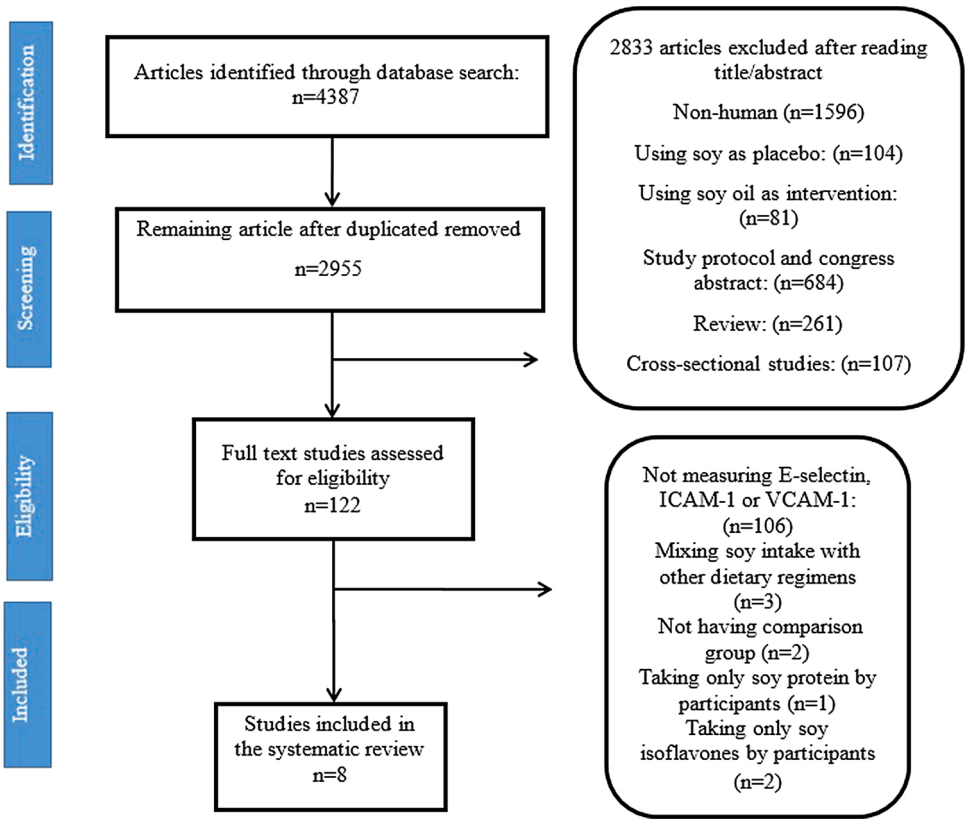

Fig. 1. Flowchart of study selection process.

[13,19,20,36–40] One article had more than one comparison group, [39] two articles had more than one intervention group, [13,37] and two other articles were conducted on separate participants. [36,40] Therefore, all these studies were reported as the separated studies. In three articles, the participants received the combination of soy isoflavones and soy protein by natural soy products. [36,38,39] Moreover, soy supplements or commercial soy products were administered in four studies[13,19,20,40] and both supplements and natural soy products were used only in one study. [37] Their treatment duration ranged from 6 to 24 weeks. Notably, soy isoflavones dose was in a range of 30–112 mg/day and soy protein dose was in a range of 11.25–52 g/day (Table 1).

3.2. Risk of bias assessment

Out of the eight RCTs included in this study, three RCTs were scored as "good" [13,20,39] and five RCTs were scored as "fair", .[19,36–3840] In addition, Four RCTs had a high risk of bias according to blinding the participants, personnel, [19,36–38] or outcome assessors. [13,20,38,40] In terms of the allocation concealment, one study had a high risk of bias. [13] The two studies performed by Liu, Z. M. et al. [20] and West, S. G. et al. [40] had bias associated with the incomplete outcome data and selective reporting, respectively. More detailed information on the quality assessment of the included RCTs are presented in Table 2.

3.3. Meta-analysis findings

In total, five RCTs with nine effect sizes were evaluated to indicate the effect of soy protein containing soy isoflavones on the serum concentrations of E-selectin (Fig. 2). As a result, the overall effect revealed a non-significant effect on the serum concentrations of E-selectin after taking soy protein in combination with soy isoflavones compared with the comparison group (WMD = 0.65, 95 % CI: -2.58, 3.89; p = 0.692). Also, a substantial heterogeneity was found among the included studies (Cochrane's Q test, $p < 0.001$; $I^2 = 91.4$ %).

The effect of soy protein containing soy isoflavones on ICAM-1 was assessed in seven studies with twelve effect sizes. According to the results of this meta-analysis, taking soy protein in combination with isoflavones had no significant effect on the serum concentrations of ICAM-1 compared with the comparison group (WMD = 2.68, 95 % CI: -0.98, 6.34; p = 0.151) (Fig. 3). Also, a significant heterogeneity was found among the included studies ($p < 0.001$; $I^2 = 67.6$ %).

Concerning the effect of soy protein containing soy isoflavones on VCAM-1, in total, eight RCTs with 15 effect sizes were included in this meta-analysis (Fig. 4). According to the results of the current meta-analysis, this combination was not significantly associated with reduction in serum concentration of VCAM-1 compared to the comparison group (WMD = 2.66, 95 % CI: -6.28, 11.61; p = 0.559). Of note, there was a significant heterogeneity among the included studies ($p < 0.001$; $I^2 = 71.3$ %).

By performing the sensitivity analysis, it was revealed that excluding each trial from the overall analysis did not cause a significant change in the overall effect size of soy protein combined with soy isoflavones on the concentrations of E-selectin, ICAM-1, and VCAM-1. Although the funnel plots for E-selectin, ICAM-1, and VCAM-1 were not visually symmetric, Begg's rank correlation and Egger's weighted regression test indicated no evidence of publication bias in this regard (E-selectin: Begg's: P = 0.536 and Egger's test: P = 0.471; ICAM-1: Begg's: P = 0.268 and Egger's test: P = 0.162; VCAM-1: Begg's: P = 0.381 and Egger's test: P = 0.613) (Fig. 5).

3.4. Subgroup analysis findings

The results of the subgroup analysis revealed that this combination reduced the concentration of E-selectin with a non-significant heterogeneity when sample size was >84 (WMD= -2.88, 95 % CI: -4.62, -1.14; p = 0.001; I^2 =40.6 %). Moreover, the heterogeneity was non-significant among those studies performed in the Americas region (p = 0.080; I^2 = 71.2 %) (Table 3). The concentration of ICAM-1 also reduced in none of the subgroup analyses (Table 4). Heterogeneity was not significant among the studies with the intervention duration >56 days (p = 0.297; I^2 = 8.00 %) as well as those studies with healthy participants (p = 0.243; I^2 = 29.40 %) (Table 4). Soy protein containing soy isoflavones decreased the serum concentration of VCAM-1 when participants' ages were ≤55 years old and the heterogeneity was not significant (WMD=-18.74, 95 % CI: -32.82, -4.66; p = 0.009; I^2 = 24.2) (Table 5). According to the results of the subgroup analysis, the heterogeneity was not significant among the studies conducted on participants with BMI > 27 (p = 0.201; I^2 = 29.8 %), the studies conducted on both male and female sex (p = 0.378; I^2 = 2.9 %), and the studies in the Americas region (p = 0.311; I^2 = 15.2 %).

4. Discussion

To the best of our knowledge, this is the first systematic review and meta-analysis performed to assess the effect of soy protein containing isoflavones on the serum CAMs. According to the results of our meta-analysis, it was shown that the combination of soy protein and soy isoflavones was not significantly associated with changes in the serum concentrations of E-selectin, ICAM-1, and VCAM-1. However, the results of the subgroup analysis revealed that the serum concentrations of E-selectin and VCAM-1 significantly decreased in the studies with a sample size >84 for E-selectin, and in the studies conducted on participants aged ≤55 years old for VCAM-1.

The results of a previous meta-analysis on 36 RCTs in 2018 revealed that soy products have no beneficial effects on the concentration of CRP in the blood. However, they suggested that using natural soy products could decrease plasma CRP more than using commercial soy products. [41] Nevertheless, finding no significant alteration in the serum levels of CAMs in this study might be due to the studied population of the included studies in the meta-analysis and their ability to produce equol. Accordingly, equol is known as one of the most important soy isoflavones and is produced from daidzein. [42] The antioxidant activity of equol was found to be stronger than other soy isoflavones and scientists have proposed that anti-inflammatory activities of soy isoflavones are

Table 2
Quality of bias assessment of the included studies according to the Cochrane guidelines.

Author name, year of publication, references	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Overall quality
Acharjee, 2015	U	U	H	U	L	L	Fair
Azadbakht, 2007	U	U	H	U	L	L	Fair
Dettmer, 2012	U	H	L	H	L	L	Good
Greany, 2008	U	U	H	U	L	L	Fair
Liu, 2013	L	L	L	H	H	U	Good
Rebholz, 2013	L	U	L	L	U	L	Good
Törmälä, 2008	U	U	H	H	L	L	Fair
West, 2005	L	U	L	H	U	H	Fair

L, low risk of bias; H, high risk of bias; U, unclear risk of bias.

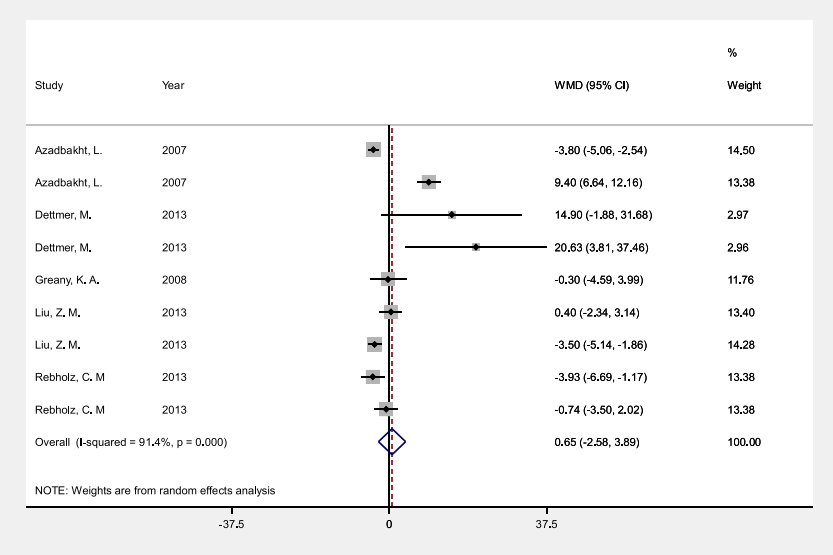

Fig. 2. Forest plot of the effect of soy protein plus soy isoflavones consumption on serum E-selectin concentrations.

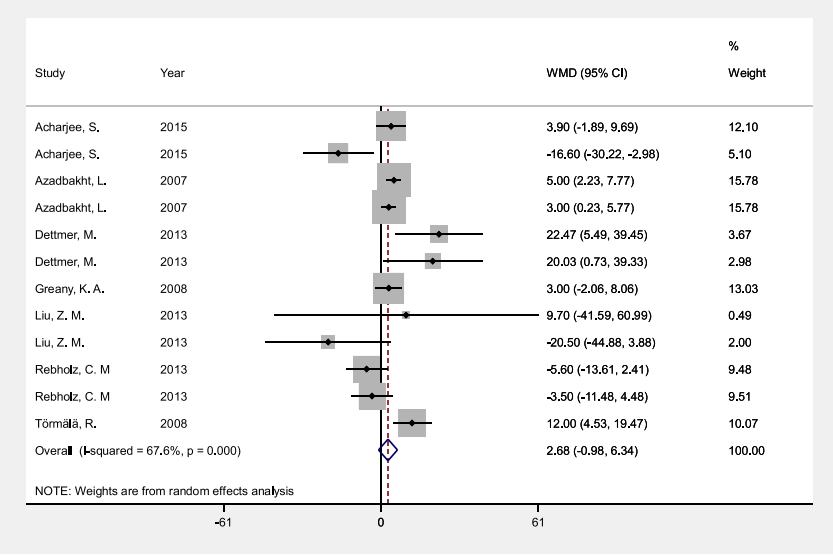

Fig. 3. Forest plot of the effect of soy protein plus soy isoflavones consumption on serum ICAM-1 concentrations.

related to some antioxidant properties. [43] In this study, we suggest that the non-significant effect of the combination containing soy protein and soy isoflavones might possibly be due to the participants' disabilities to produce equol. Of 15 datasets investigated in this meta-analysis, eight datasets were conducted in Western countries and no dataset was done by Japanese or Korean researchers. In western countries, it was reported that less than 30 % of the adults can produce equol, but in Asia, and particularly in Japan and Korea, at least 50 % of adults are equol producers. [44] Unfortunately, most of the included articles in this meta-analysis reported no information on the equol production.

According to the results of the subgroup analysis, it was indicated that the studies with a larger sample size could more reduce the serum concentration of E-selectin. It might be possible that the small sample size in some of these RCTs caused an insufficient statistical power to find any significant difference.

In the two studies conducted on participants with metabolic syndrome [37] and hypertension, [39] the serum levels of E-selectin significantly decreased and in another study performed on participants with metabolic syndrome, the serum concentration of ICAM-1 showed a significantly decrease. [36] Therefore, the absence of an intervention effect may be associated with participants' health status. In this study, most of the included articles were conducted on healthy participants with low levels of inflammation, so there may be less room for the improvement resulted from taking soy protein combined with soy isoflavones.

In this meta-analysis, a significant heterogeneity was detected in the included studies and even in all the subgroup analyses. We suggested that the probable reasons for this heterogeneity might be various sources of soy protein and soy isoflavones among the included studies, and selecting participants from different countries with different abilities to produce equol, different life style, and different health statuses.

The findings also showed various limitations to the research engagement. Firstly, a few numbers of studies for all outcomes, especially in the subgroup analysis, were included in this study. Therefore, the results obtained in the present study could be biased by sample size. Secondly, a significant heterogeneity was observed in these included articles and even in all the subgroup analyses. Thirdly, since most of the included articles provided no information regarding equol production, we did not assess whether equol production is able to change the overall

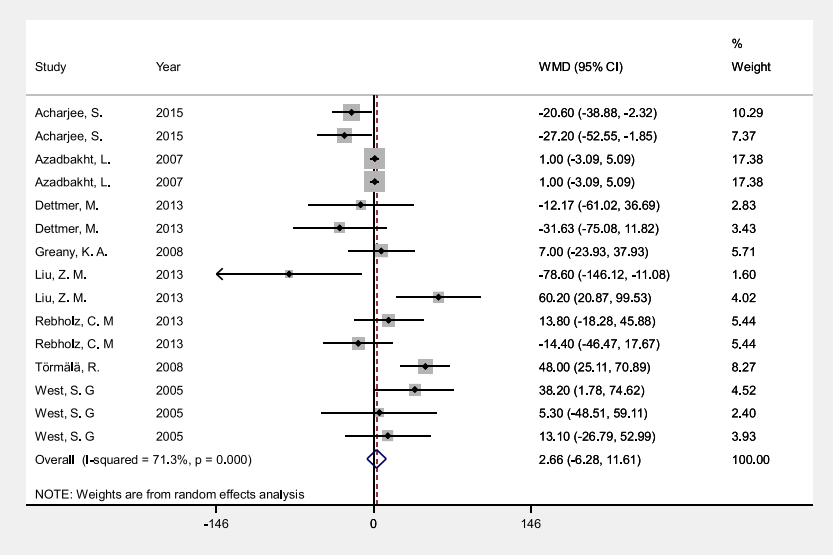

Fig. 4. Forest plot of the effect of soy protein plus soy isoflavones consumption on serum VCAM-1 concentrations.

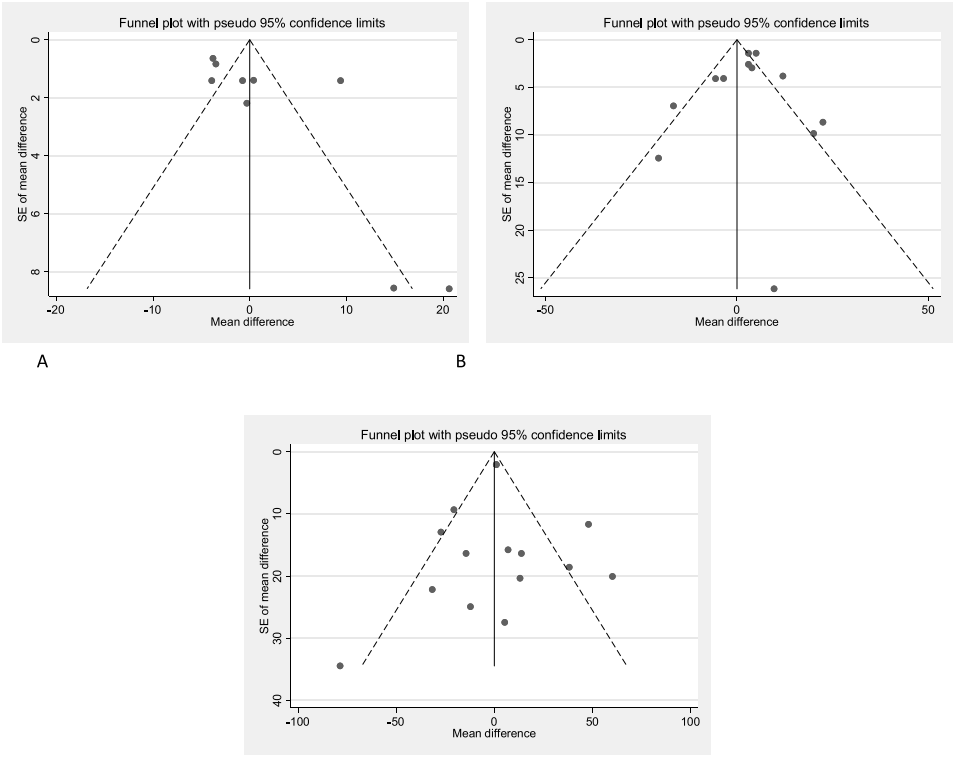

Fig. 5. Funnel plots for the publication bias. A: Studies of the effects of soy protein plus soy isoflavones consumption on serum E-selectin concentrations. B: Studies of the effects of soy protein plus soy isoflavones consumption on serum ICAM-1 concentrations. C: Studies of the effects of soy protein plus soy isoflavones consumption on serum VCAM-1 concentrations.

results of meta-analysis. Next, a few numbers of subjects were involved in most of these articles. As another limitation, the intervention duration in most articles was short (8 weeks), and only one study followed participants for 24 weeks. Finally, most of the RCTs were conducted in the Americas region; therefore, the effect of soy protein combined with soy isoflavones among Eastern populations remains questionable yet.

Our study also had several strengths. We did not limit our search to a specific publication time. We removed the RCTs in which the subjects consumed other nutrients besides soy protein and soy isoflavones in the intervention group; therefore, their confounding effects were excluded as well. Moreover, our meta-analysis is the first article that examined the effect of the combination of soy protein combined with soy isoflavones on the CAMs. Finally, we indicated the effects of soy protein dose; soy isoflavones dose; BMI; age; sex; geographical region; sample size; trial design; health status; intervention duration; publication year; baseline levels of E-selectin, ICAM-1, and VCAM-1; and quality assessment on the

Table 3
Subgroup analyses for studies evaluating the effect of soy protein plus soy isoflavones on serum E-selectin.

	Subgroup	No. of trial	Change in E-selectin (95 % CI)	P-value	I^2 (%)	$P_{heterogeneity}$
Total	–	9	0.65 (-2.58, 3.89)	0.692	91.4	<0.001
Soy isoflavones dose	≤89.5 mg/d	5	−2.22 (-4.45, 0.01)	0.051	61.5	0.034
	>89.5 mg/d	4	4.21 (-3.10, 11.53)	0.259	95.06	<0.001
Soy protein dose	≤18 g/d	6	2.63 (-2.23, 7.49)	0.289	94.5	<0.001
	>18 g/d	3	−1.89 (-4.23, 0.46)	0.114	39.0	<0.001
Design	Parallel	4	1.70 (-3.77, 7.17)	0.542	82.3	0.001
	Cross-over	5	0.09 (-4.76, 4.94)	0.971	94.7	<0.001
Intervention duration	≤56 day	7	2.10 (-2.68, 6.87)	0.390	93.1	<0.001
	>56 day	2	−1.71 (-5.52, 2.10)	0.379	82.6	0.017
Baseline E-selectin	≤38 ng/mL	4	−0.27 (-4.12, 3.58)	0.891	78.1	0.003
	>38 ng/mL	5	1.30 (-4.26, 6.86)	0.647	95	<0.001
Health status	Healthy	1	0.40 (-2.34, 3.14)	0.775	–	–
	At risk/disease	8	0.80 (-2.86, 4.46)	92.3	0.668	<0.001
Sample size	≤84	6	4.01 (-1.92, 9.93)	0.185	94.1	<0.001
	>84	3	−2.88 (-4.62, -1.14)	0.001	40.6	0.186
Geographical Region	Americas	5	0.32 (-3.85, 4.49)	0.881	71.2	0.080
	Europe	–	–	–	–	–
	Asia	4	0.50 (-4.45, 5.46)	0.842	96.2	<0.001
Sex	Female	5	0.35 (-3.95, 4.66)	0.873	95	<0.001
	Male	–	–	–	–	–
	Both	4	1.41 (-4.35, 7.18)	0.631	77.8	0.004
Age	≤49 years	4	1.41 (-4.35, 7.18)	0.631	77.8	0.004
	>49 year	3	−1.42(-4.30, 1.46)	0.333	69.9	0.036
	Unknown	2	2.74 (-10.19, 15.68)	0.678	98.6	<0.001
BMI	≤27.5	5	0.69 (-3.42, 4.8)	0.743	77.3	0.001
	>27.5	4	0.18 (-5.52, 5.89)	0.949	96	<0.001
	Unknown	5	−0.01 (-0.18, 0.17)	0.949	79.0	0.001
Quality assessment	Good	6	−0.98 (-3.81, 1.84)	0.495	74.4	0.002
	Fair	3	1.75 (-7.24, 10.73)	0.703	97.3	<0.001
	Weak	–	–	–	–	–
Publication year of article	≤2010	3	1.75 (-7.24, 10.73)	0.703	97.3	<0.001
	>2010	6	−0.98 (-3.81, 1.84)	0.495	74.4	0.002

BMI: Body Mass Index, ng/mL: nanograms per milliliter, mg/d: milligram per day, g/d: gram per day, CI: confidence interval.

Table 4
Subgroup analyses for studies evaluating the effect of soy protein plus soy isoflavones on serum ICAM-1.

	Subgroup	No. of trial	Change in ICAM-1 (95 % CI)	P-value	I^2 (%)	$P_{heterogeneity}$
Total	–	12	2.68 (-0.98, 6.34)	0.151	67.6	<0.001
Soy isoflavones dose	≤95 mg/d	6	3.38 (-2.06, 8.83)	0.223	70	0.005
	>95 mg/d	6	1.28 (-5.40, 7.95)	0.708	71	0.004
Soy protein dose	≤22 g/d	6	5.34 (0.48, 10.21)	0.031	58.5	0.034
	>22 g/d	6	0.15 (-5.84, 6.13)	0.961	74.8	0.001
Design	Parallel	4	9.0 (-11.92, 29.92)	0.399	66.5	0.030
	Cross-over	8	2.02 (-1.38, 5.41)	0.245	68.9	0.002
intervention duration	≤56 day	10	3.12 (-0.50, 6.74)	0.910	70.2	<0.001
	>56 day	2	−14.17 (-38.26, 9.91)	0.249	8.00	0.297
Baseline ICAM	≤266 ng/mL	6	5.55 (-1.87, 12.96)	0.143	75.7	0.001
	>266 ng/mL	6	1.73 (-2.51, 5.97)	0.424	62.7	0.020
Health status	Healthy	3	7.42 (1.17, 13.68)	0.020	29.4	0.243
	At risk/disease	9	1.19 (-3.12, 5.51)	0.558	72	<0.001
Sample size	≤78	6	7.10 (-2.89, 17.09)	0.164	75	0.001
	>78	6	1.42 (-2.07, 4.91)	0.424	60.5	0.027
Geographical Region	Americas	5	3.83 (-4.20, 11.86)	0.350	72	0.007
	Europe	1	12 (4.53, 19.47)	0.002	–	–
	Asia	6	1.73 (-2.51, 5.97)	0.424	62.7	0.02
Sex	Female	8	3.24 (-0.26, 6.75)	0.07	61.6	0.011
	Male	–	–	–	–	–
	Both	4	5.69 (-6.63, 18.10)	0.365	77.7	0.004
Age	≤54.5 years	5	5.68 (5.90, 17.25)	0.336	70.6	0.009
	>54.5 year	5	0.46 (-7.39, 8.30)	0.909	76.6	0.002
	Unknown	2	4.00 (2.04, 5.96)	<0.001	0	0.317
BMI	≤27.2	6	6.19 (-0.32, 12.7)	0.063	59.5	0.03
	>27.2	6	0.22 (-4.63, 5.08)	0.928	74.9	0.001
Quality assessment	Good	6	2.61 (-8.49, 13.71)	0.645	69.1	0.006
	Fair	6	3.73 (-0.38, 7.08)	0.029	65.1	0.014
	Weak	–	–	–	–	–
Publication year of article	≤2010	4	4.64 (2, 7.27)	0.001	44.7	0.143
	>2010	8	0.06 (-8.07, 8.19)	0.989	70.6	0.001

ICAM-1: Intercellular Adhesion Molecule-1, BMI: Body Mass Index, ng/mL: nanograms per milliliter, mg/d: milligram per day, g/d: gram per day, CI: confidence interval.

Table 5
Subgroup analyses for studies evaluating the effect of soy protein plus soy isoflavones on serum VCAM-1.

	Subgroup	No. of trial	Change in VCAM-1 (95 % CI)	P-value	I^2 (%)	$P_{heterogeneity}$
Total	–	15	2.66 (-6.28, 11.61)	0.559	71.3	<0.001
Soy isoflavones dose	≤90 mg/d	9	3.38 (-2.06, 8.83)	0.223	70	0.005
	>90 mg/d	6	2.24 (-21.78, 26.25)	0.855	87.6	<0.001
Soy protein dose	≤25 g/d	4	−2.12 (-11.17, 6.93)	0.647	67.6	0.001
	>25 g/d	11	15.05 (-12.89, 42.99)	0.291	72.7	0.012
Design	Parallel	4	−12.04 (-68.65, 44.56)	0.677	81.8	0.001
	Cross-over	11	2.88 (-5.54, 11.31)	0.503	69.1	<0.001
Intervention duration	≤56 day	2	1.45 (-6.75, 9.64)	0.729	65.5	<0.001
	>56 day	13	−6.37 (-142.28, 129.53)	0.927	91.7	<0.001
Baseline VCAM	≤568 ng/mL	7	9.26 (-1.32, 19.84)	0.086	78	<0.001
	>568 ng/mL	8	−6.62 (-24.84, 11.6)	0.476	59.8	0.015
Health status	Healthy	5	−1.50 (-40.38, 37.38)	0.940	85.2	<0.001
	At risk/disease	10	1.43 (-6.46, 9.33)	0.722	58.2	0.01
Sample size	≤68	8	6.80 (-28.28, 14.67)	0.535	56	0.026
	>68	7	6.22 (-3.88, 16.33)	0.227	81	<0.001
Geographical Region	Americas	8	4 (-10.57, 18.56)	0.591	15.2	0.311
	Europe	1	48 (25.11, 70.89)	<0.001	–	–
	Asia	6	−3.88 (-13.77, 6.02)	0.443	79.1	<0.001
Sex	Female	10	3.04 (-7, 13.09)	0.552	78	<0.001
	Male	1	38.20 (1.78, 74.62)	0.04	–	–
	Both	4	−7.86 (-26.77, 11.06)	0.416	2.9	0.378
Age	≤55 years	7	−18.74 (-32.82, -4.66)	0.009	24.2	0.244
	>55 year	6	31.22 (12.77, 49.67)	0.001	39.4	0.143
	Unknown	2	1 (-1.89, 3.89)	0.498	0	1
BMI	≤27	8	12.99 (-14.07, 40.05)	0.347	80.8	<0.001
	>27	7	−0.63 (-5.6, 4.33)	0.802	29.8	0.201
Quality assessment	Good	6	−5.8 (-37.91, 26.32)	0.724	72.2	0.003
	Fair	9	3.34 (-5.74, 12.43)	0.471	74	<0.001
	Weak	–	–	–	–	–
Publication year of article	≤2010	7	9.13 (0.16, 18.09)	0.046	70.3	0.003
	>2010	8	−10.65 (-32.09, 10.78)	0.330	68.5	0.002

VCAM-1: Vascular Cell Adhesion Protein-1, BMI: Body Mass Index, ng/mL: nanograms per milliliter, mg/d: milligram per day, g/d: gram per day, CI: confidence interval.

effect size of soy protein combined with soy isoflavones.

5. Conclusion

According to the results of our meta-analysis, the combination of soy protein and soy isoflavones could not decrease the serum concentrations of E-selectin, ICAM-1, and VCAM-1. To confirm the results of the current study, we still need more RCTs with high quality, large sample size, longer intervention period, done on unhealthy participants, and in different parts of the world. Future studies should assess the effect of soy protein combined with soy isoflavones on equol and non-equol producers separately and also measure the serum concentration of equol before and after the intervention.

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Declaration of Competing Interest

The authors report no declarations of interest.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.ctim.2021.102764.

References

1 Farmer JA, Torre-Amione G. The renin angiotensin system as a risk factor for coronary artery disease. *Curr Atheroscler Rep*. 2001;3(2):117–124.
2 Fuster V, Kelly BB, eds. *Promoting cardiovascular health in the developing world*. Institute of Medicine; 2010.
3 Farsi F, Heshmati J, Keshtkar A, et al. Can coenzyme Q10 supplementation effectively reduce human tumor necrosis factor-α and interleukin-6 levels in chronic inflammatory diseases? A systematic review and meta-analysis of randomized controlled trials. *Pharmacol Res*. 2019;148, 104290.
4 Popa C, Netea MG, van Riel PLCM, van der Meer JWM, Stalenhoef AFH. The role of TNF-α in chronic inflammatory conditions, intermediary metabolism, and cardiovascular risk. *J Lipid Res*. 2007;48(4):751–762.
5 Yamamoto K, Ando J. New molecular mechanisms for cardiovascular disease:Blood flow sensing mechanism in vascular endothelial cells. *J Pharmacol Sci*. 2011;116(4):323–331.
6 Schleimer RP, Rutledge BK. Cultured human vascular endothelial cells acquire adhesiveness for neutrophils after stimulation with interleukin 1, endotoxin, and tumor-promoting phorbol diesters. *J Immunol*. 1986;136(2):649–654.
7 Ley K, Laudanna C, Cybulsky MI, Nourshargh S. Getting to the site of inflammation: The leukocyte adhesion cascade updated. *Nat Rev Immunol*. 2007;7(9):678–689.
8 Haghighatdoost F, Hariri M. Can resveratrol supplement change inflammatory mediators? A systematic review and meta-analysis on randomized clinical trials. *Eur J Clin Nutr*. 2019;73(3):345–355.
9 Haghighatdoost F, Hariri M. The effect of alpha-lipoic acid on inflammatory mediators: A systematic review and meta-analysis on randomized clinical trials. *Eur J Pharmacol*. 2019;849:115–123.
10 King DE. Dietary fiber, inflammation, and cardiovascular disease. *Mol Nutr Food Res*. 2005;49(6):594–600.
11 Khiaosa-Ard R, Zebeli Q. Diet-induced inflammation: From gut to metabolic organs and the consequences for the health and longevity of ruminants. *Res Vet Sci*. 2018;120:17–27.
12 Ramdath DD, Padhi EM, Sarfaraz S, Renwick S, Duncan AM. Beyond the cholesterol-lowering effect of soy protein: A review of the effects of dietary soy and its constituents on risk factors for cardiovascular disease. *Nutrients*. 2017;9(4).
13 Dettmer M, Alekel DL, Lasrado JA, et al. The effect of soy protein beverages on serum cell adhesion molecule concentrations in prehypertensive/stage 1 hypertensive individuals. *J Am Coll Nutr*. 2012;31(2):100–110.
14 Atteritano M, Marini H, Minutoli L, et al. Effects of the phytoestrogen genistein on some predictors of cardiovascular risk in osteopenic, postmenopausal women: a two-year randomized, double-blind, placebo-controlled study. *J Clin Endocrinol Metab*. 2007;92(8):3068–3075.

15 Yan G, You B, Chen SP, Liao JK, Sun J. Tumor necrosis factor-alpha downregulates endothelial nitric oxide synthase mRNA stability via translation elongation factor 1-alpha 1. *Circ Res*. 2008;103(6):591–597.
16 Jelic S, Lederer DJ, Adams T, et al. Vascular inflammation in obesity and sleep apnea. *Circulation*. 2010;121(8):1014–1021.
17 Scheller J, Chalaris A, Schmidt-Arras D, Rose-John S. The pro- and anti-inflammatory properties of the cytokine interleukin-6. *Biochim Biophys Acta*. 2011;1813(5):878–888.
18 Sacks FM, Lichtenstein A, Van Horn L, Harris W, Kris-Etherton P, Winston M. Soy protein, isoflavones, and cardiovascular health: An American Heart Association Science Advisory for professionals from the Nutrition Committee. *Circulation*. 2006;113(7):1034–1044.
19 Greany KA, Nettleton JA, Wangen KE, Thomas W, Kurzer MS. Consumption of isoflavone-rich soy protein does not alter homocysteine or markers of inflammation in postmenopausal women. *Eur J Clin Nutr*. 2008;62(12):1419–1425.
20 Liu ZM, Ho SC, Chen YM, Woo J. Effect of soy protein and isoflavones on blood pressure and endothelial cytokines: A 6-month randomized controlled trial among postmenopausal women. *J Hypertens*. 2013;31(2):384–392.
21 Miyamoto N, Mandai M, Suzuma I, Suzuma K, Kobayashi K, Honda Y. Estrogen protects against cellular infiltration by reducing the expressions of E-selectin and IL-6 in endotoxin-induced uveitis. *J Immunol*. 1999;163(1):374–379.
22 Pfeilschifter J, Köditz R, Pfohl M, Schatz H. Changes in proinflammatory cytokine activity after menopause. *Endocr Rev*. 2002;23(1):90–119.
23 Ito A, Bebo Jr BF, Matejuk A, et al. Estrogen treatment down-regulates TNF-alpha production and reduces the severity of experimental autoimmune encephalomyelitis in cytokine knockout mice. *J Immunol*. 2001;167(1):542–552.
24 Chacko BK, Chandler RT, Mundhekar A, et al. Revealing anti-inflammatory mechanisms of soy isoflavones by flow: Modulation of leukocyte-endothelial cell interactions. *Am J Physiol Heart Circ Physiol*. 2005;289(2):H908–15.
25 Jia Z, Babu PV, Si H, et al. Genistein inhibits TNF-α-induced endothelial inflammation through the protein kinase pathway A and improves vascular inflammation in C57BL/6 mice. *Int J Cardiol*. 2013;168(3):2637–2645.
26 Su Y, Simmen RC. Soy isoflavone genistein upregulates epithelial adhesion molecule E-cadherin expression and attenuates beta-catenin signaling in mammary epithelial cells. *Carcinogenesis*. 2009;30(2):331–339.
27 Beavers KM, Jonnalagadda SS, Messina MJ. Soy consumption, adhesion molecules, and pro-inflammatory cytokines: A brief review of the literature. *Nutr Rev*. 2009;67(4):213–221.
28 Sakamoto Y, Kanatsu J, Toh M, Naka A, Kondo K, Iida K. The dietary isoflavone daidzein reduces expression of pro-inflammatory genes through PPARalpha/gamma and JNK pathways in Adipocyte and macrophage Co-cultures. *PLoS One*. 2016;11(2),e0149676.
29 Hernandez-Montes E, Pollard SE, Vauzour D, et al. Activation of glutathione peroxidase via Nrf1 mediates genistein's protection against oxidative endothelial cell injury. *Biochem Biophys Res Commun*. 2006;346(3):851–859.
30 Higgins J, Green S. *Cochrane handbook for systematic reviews, version 5.0.2*. Joh Wiley & Sons Ltd: The Cochrane Collaboration; 2009.
31 Hozo SP, Djulbegovic B, Hozo I. Estimating the mean and variance from the median, range, and the size of a sample. *BMC Med Res Methodol*. 2005;5(1):13.
32 DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials*. 1986;7(3):177–188.
33 Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med*. 2002;21(11):1539–1558.
34 Begg CB, Berlin JA. Publication bias and dissemination of clinical research. *JNCI: Journal of the National Cancer Institute*. 1989;81(2):107–115.
35 Egger M, Smith GD, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *Bmj*. 1997;315(7109):629–634.
36 Acharjee S, Zhou JR, Elajami TK, Welty FK. Effect of soy nuts and equol status on blood pressure, lipids and inflammation in postmenopausal women stratified by metabolic syndrome status. *Metabolism*. 2015;64(2):236–243.
37 Azadbakht L, Kimiagar M, Mehrabi Y, Esmaillzadeh A, Hu FB, Willett WC. Soy consumption, markers of inflammation, and endothelial function - A cross-over study in postmenopausal women with the metabolic syndrome. *Diabetes Care*. 2007;30(4):967–973.
38 Törmälä R, Appt S, Clarkson TB, et al. Impact of soy supplementation on sex steroids and vascular inflammation markers in postmenopausal women using tibolone: Role of equol production capability. *Climacteric*. 2008;11(5):409–415.
39 Rebholz CM, Reynolds K, Wofford MR, et al. Effect of soybean protein on novel cardiovascular disease risk factors: A randomized controlled trial. *Eur J Clin Nutr*. 2013;67(1):58–63.
40 West SG, Hilpert KF, Juturu V, et al. Effects of including soy protein in a blood cholesterol-lowering diet on markers of cardiac risk in men and in postmenopausal women with and without hormone replacement therapy. *J Womens Health*. 2005;14(3):253–262, 2002.
41 Khodarahmi M, Jafarabadi MA, Moludi J, Farhangi MA. A systematic review and meta-analysis of the effects of soy on serum hs-CRP. *Clin Nutr*. 2019;38(3):996–1011.
42 Setchell KD, Clerici C. Equol: history, chemistry, and formation. *J Nutr*. 2010;140(7):1355s–1362s.
43 Messina M. Soy and health update: evaluation of the clinical and epidemiologic literature. *Nutrients*. 2016;8(12).
44 Setchell KD, Clerici C. Equol: Pharmacokinetics and biological actions. *J Nutr*. 2010;140(7):1363s–1368s.