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REVIEW

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Can soy isoflavones in combination with soy protein change serum levels of C-reactive protein among patients with chronic inflammatory diseases? A systematic review and meta-analysis on randomized controlled trials

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Abstract

Background C-reactive protein (CRP) is one of the most important markers for assessing inflammation status and its increased concentration in blood is associated with many chronic diseases in humans. The aim of this study was to reveal the effect of soy isoflavones containing soy protein on serum levels of CRP in adult population with chronic inflammatory diseases.

Materials and methods We searched databases including PubMed, Cochrane Library, ISI Web of Science, Scopus, and clinicalTrials.gov up to March 2025. We used random effects model to calculate the heterogeneity and the overall effects.

Results Twenty-seven articles were involved in the systematic review and twenty-two articles with thirty-four effect sizes were considered for meta-analysis. The overall estimates revealed that soy isoflavones containing soy protein significantly decreased serum levels of CRP in comparison with control group (weighted mean difference (WMD)= -0.49 mg/L; 95% confidence interval (CI): -0.74, -0.25; $P=0<0.001$).

Conclusion Although our results clearly showed soy isoflavones containing soy protein can have decreasing effect on inflammation in participants with chronic inflammatory disease, more large-scale and high quality interventional studies still need to be done to clarify our results.

Keywords C-reactive protein, Soy isoflavones, Soy protein, Systematic review, Meta-analysis

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Introduction

Inflammation is known by the enhancement of serum levels of inflammatory mediators during tissue injury [1]. Inflammatory process causes the increased levels of acute phase cytokines such as C-reactive protein (CRP), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-α) [2–4].

Soy, which is popular in Asian countries, is beneficial in the prevention of many chronic diseases caused by inflammation such as cardiovascular diseases (CVDs), obesity, cancer, and diabetes [5–7]. Beneficial effects of soy might be due to its two components, isoflavones and proteins.

CRP predicts the incidence of many chronic diseases [8–10]. Moreover, CRP is the best clinical indicators for assessing health status and the risks caused by acute inflammation [11]. New evidence revealed one reason for increased levels of CRP is the enhancement of reactive oxygen species (ROS) [12]. Considering the results of in vitro studies, scientists have evinced anti-oxidant activities of soy isoflavones [13], and considered isoflavones as possible anti-inflammatory agents. Moreover, soy isoflavones act as dietary agents for the prevention of cell-mediated inflammatory reaction and the signal transduction instilled by cytokine in immune cells [14, 15].

Besides isoflavones, soy-derived peptides seem to have anti-inflammatory effects [16]. Some studies have shown the antioxidant, immunomodulatory, and anticancer characteristics of soy peptides [17]. New evidence also suggests a reduced effectiveness of other nutrients in the human body [18–23].

According to this evidence, scientists assessed the effect of soy isoflavones containing protein on serum levels of CRP through randomized clinical trials (RCTs), but their results are not conclusive [24–28]. Some researchers attempted to carry out systematic reviews and meta-analyses on the impact of soy on inflammation, but they either overlooked the combination of soy isoflavones with soy protein [29, 30] or failed to focus their meta-analysis on individuals with chronic illnesses [31]. Given that the outcomes of these RCTs are inconsistent and health status could play a crucial role in determining the benefits of soy isoflavones combined with protein—and since no meta-analysis has evaluated the combined effect of soy isoflavones and soy protein—we chose to compile the findings of RCTs specifically among participants suffering from chronic inflammatory diseases through a systematic review. Additionally, we aimed to measure the effect of soy isoflavones combined with protein on CRP by conducting a meta-analysis.

Materials and methods

The results of our systematic review are reported based on PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) checklists [32]. Moreover, we registered the protocol in PROSPERO (No. CRD42020166053).

Literature search

Databases including PubMed, Cochrane Library, ISI Web of Science, Scopus, and clinicalTrials.gov were systematically searched up to March 2025 to find papers assessing the effect of soy isoflavones containing protein on CRP levels among adult population suffering from chronic inflammatory diseases.

Since serum levels of CRP were investigated as primary outcomes and taking soy isoflavones containing protein was the exposure variable in this study, databases were searched with the following main keywords: "C-reactive protein", "Phytoestrogens", "Soy Foods", "Genistein", "Soybean proteins", "Isoflavones", and "Equol". We presented all used keywords for searching these databases in supplementary Table 1. Since it is possible to miss a few articles when searching databases with only CRP, we designed our search strategy with the most important inflammatory mediators. Afterward, the search strategy was designed using quotation marks, parentheses, Boolean operators, and asterisks. The databases search was conducted independently by two reviewers (MH and AGh). The results of a systematic search from different databases were combined in EndNote X9 software and duplicate papers were excluded. Then, the titles and abstracts of all the found articles were checked by two independent reviewers (MH and BA) to find the relevant RCTs. Further related studies were searched by a manual screening of the reference lists of all the found RCTs, meta-analyses, and review publications to find further relevant studies on soy products. In this study, we did not limit our search by specific date of publication and solved any discrepancies by group discussion.

Study eligibility criteria

In this study we used PICOS (Patient/Population, Intervention, Comparison, Outcome, Study types) framework as inclusion criteria: (I) Population: subjects with chronic inflammatory diseases and age ≥ 18 years old (diseases with slow, long-term inflammation lasting for prolonged periods of several months to years); (II) Intervention: natural or commercial form of soy isoflavones containing protein; (III) Comparison: participants received the placebo or current standard treatment to provide a comparison to the intervention group; (IV) Outcome: changes in CRP levels; (V) Study design: RCTs written in English.

After their full text had been read fully, the RCTs with the following criteria were excluded: (1) used other

dietary supplements besides soy isoflavones and soy protein; (2) did not present any information about CRP levels at the beginning or at the end of intervention and data how to compute it; (3) not having comparison group; (4) showed CRP levels in figures; (5) not reporting soy isoflavones dose or soy protein dose in natural soy products; (6) were not written in English.

Data extraction

Two researchers (MH and BA) independently scanned the articles for eligible RCTs using a form which contains the following information: name of first author, year of publication, country, sex, body mass index (BMI), sample size in intervention and comparison groups, parallel or crossover design and other details regarding study design, mean/median/range of age, dose of soy isoflavones and soy protein and their sources, intervention duration, mean of CRP and its standard deviation (SD). Moreover, in this study the CRP was converted to a same unit (mg/L). Group discussions were performed to assess and resolve the problems that the reviewers met in this step. Papers with more than one intervention or comparison group were deemed as separate studies in this study. Any unclear information was clarified by sending emails to corresponding authors.

Quality assessment

Quality assessment for selected studies was done independently by two reviewers (MH and AGh), according to the guidance provided by the Cochrane Handbook [33]. The considered criteria were the concealment of allocation, the random sequence generation, blinding for personnel, participants and outcome assessment, reporting outcome data incompletely, and reporting outcome data selectively. The article quality was assessed in conformity with each criteria judgment. RCTs were scored as good if they had a low risk for at least three items, as fair if they had a low risk for at least two items, and as weak if they had less than two items with low risk of bias.

Data synthesis and statistical analysis

The analyses were conducted using the mean differences (MDs) of CRP (mg/L) and their SDs according to the Cochrane handbook [34]. When there were the RCTs that did not provide MDs and SDs values, we calculated them from other data that were reported in those papers. Each effect size for CRP was computed using mean changes from the baseline and its SDs for both comparison and intervention groups. In the case of reporting a standard error (SE), SD was computed by multiplying SE in square root of the sample size. Furthermore, Hozo method was applied to calculate the mean concentration of CRP when median or range were only reported [35]. We used random effects model to calculate the heterogeneity and the overall effects [36]. Heterogeneity of intervention effects was specified through I-squared statistic and Cochran's Q test. Heterogeneity with p-value ≤ 0.10 based on Cochran's Q test and I-squared statistic $\geq 50\%$ was considered significant. We included 95% confidence intervals (CIs) for all calculated effect sizes. The source of heterogeneity was investigated via subgroup analyses based on sex, age, BMI, isoflavones dose, trial design, baseline CRP (mg/l), intervention duration, sample size, geographical region, quality assessment, and publication year of the article. Meta-regression analysis was used to adjust the effect of afore-mentioned variables on the effect sizes. Publication bias was examined using funnel plots, Begg's rank correlation test, and Egger's regression asymmetry tests [37]. The leave-one out method was also used to evaluate the effect of each study on the overall effect size (Sensitivity analysis). All analyses were conducted using STATA software version 15 (Stata Corp, College Station, TX).

Results

Following a multi-database search, 7012 articles were found. Through excluding duplicates, 4412 articles remained for reading titles and abstracts. Through screening titles and abstracts, 4261 articles were excluded due to different reasons including: using soy oil as intervention, using soy as placebo, non-human studies, having participants under 18, study protocol, congress abstract, reviews and cross-sectional studies. Thus, 151 articles remained to go through the full text to check for inclusion and exclusion criteria. After considering those criteria, 124 articles were removed base on the following reasons: (1) not measuring CRP ($n=48$), (2) combining soy intake with other dietary regimens ($n=19$), (3) consuming only soy protein by participants ($n=2$), (4) consuming only soy isoflavones by participants ($n=24$), (5) not having comparison group ($n=6$), (6) conducting on healthy participants ($n=18$), (7) not reporting dose of soy isoflavones and soy protein ($n=7$). Out of twenty-seven RCTs included in our systematic review [24–28, 38–59], two articles did not provide enough data [44, 46], and three articles had very large effect sizes to be taken in our meta-analysis [38, 54, 55]. Therefore, twenty-two articles with thirty-four effect sizes were used in this meta-analysis [24–28, 39–43, 45, 47–53, 56–59]. Study selection is shown in Fig. 1.

Study characteristics

The details of the study characteristics are described in Table 1.

Regarding intervention periods and the number of intervention and comparison groups, two studies had two comparison groups [27, 48], one study had two intervention groups (men and women were assessed separately) [42], and two studies assessed CRP levels in

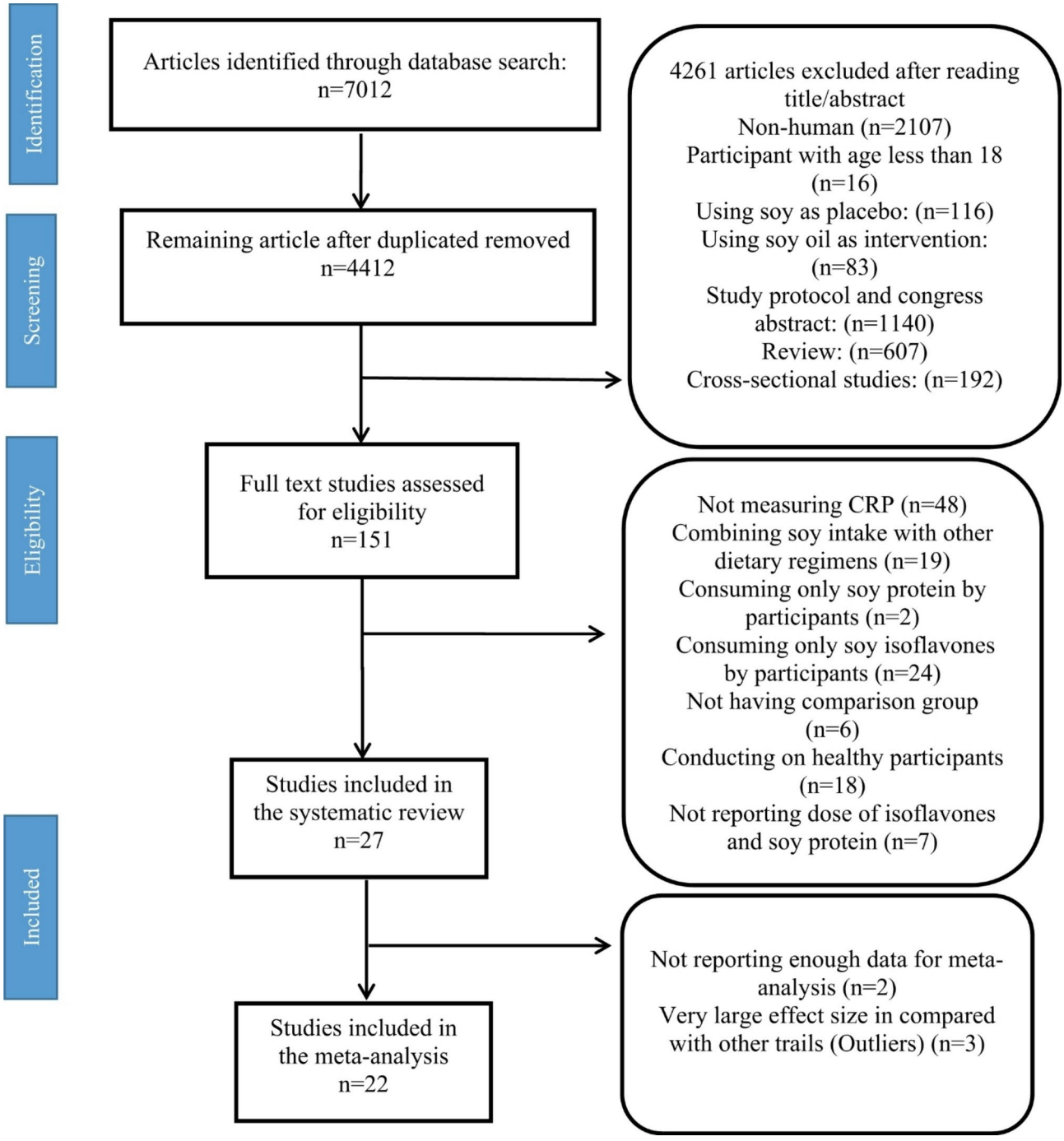


Fig. 1 Flowchart of study selection process

2 intervals during the intervention period [38, 56]. On the subject of the form and amount of the soy intake, two studies reported using two different forms of soy [39, 40] and three studies used two different amounts [42, 50, 54]. Each article was considered as two articles with separate effect sizes. In one study, three different forms of soy [44] and in another study, four different amounts of soy [25] were assessed; therefore, these articles were considered as three and four articles with separate effect sizes, respectively.

Concerning the trial design, fourteen studies had crossover [24, 28, 39, 42, 44–52, 59] and thirteen studies had parallel design [25–27, 38, 40, 41, 43, 53–58]. Intervention doses for soy isoflavones and soy protein were 6.2–150 mg/d and 6.5–60 gr/d, respectively; and intervention duration ranged from 4 to 192 weeks. Regarding

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$^{\Delta}$	Intervention	Placebo	Duration (week)	Results
1 Acharjee, S. 2015 Israel	Postmenopausal women with metabolic syndrome *N* = 11	Age: 54.1 ± 6.5 BMI: 31.8 ± 4.6	Randomized, controlled, crossover trial	0.5 cups/day soy nuts (containing 25 g of soy protein and 101 mg of aglycone isoflavones)	Non soy protein	8	CRP† decreased significantly
2.1 Anderson, J. W. 2007 USA	Obese women *N* = 43	Age: 46.5 ± 8.4 BMI: 34.6 ± 3.6	Randomized, single blind controlled trial	Soy Shakes containing 150 mg/day isoflavones and 60 mg/day protein	Casein shakes	8	CRP did not change significantly
2.2 Anderson, J. W. 2007 USA	Obese women *N* = 43	Age: 46.5 ± 8.4 BMI: 34.6 ± 3.6	Randomized, single blind controlled trial	Soy Shakes containing 150 mg/day isoflavones and 60 mg/day protein	Casein shakes	16	CRP did not change significantly
3.1 Azadbakht, L. 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)	Read meat	8	CRP decreased significantly
3.2 Azadbakht, L. 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 (containing 15 g/day protein with 102 mg/day isoflavones)	Read meat	8	CRP decreased significantly
4.1 Azadbakht, L. 2008 Iran	Type 2 diabetes with nephropathy *N* = 41 F = 23 M = 18	Age: 62.0 ± 12.0 BMI: N/M	Randomized clinical trial	Diet containing 16 ± 9 g/day soy protein and 43 ± 15 mg/day soy isoflavones	Control diet	48	CRP did not change significantly
4.2 Azadbakht, L. 2008 Iran	Type 2 diabetes with nephropathy *N* = 41 F = 23 M = 18	Age: 62.0 ± 12.0 BMI: N/M	Randomized clinical trial	Diet containing 17 ± 11 g/day soy protein and 48 ± 19 mg/day soy isoflavones	Control diet	96	CRP did not change significantly
4.3 Azadbakht, L. 2008 Iran	Type 2 diabetes with nephropathy *N* = 41 F = 23 M = 18	Age: 62.0 ± 12.0 BMI: N/M	Randomized clinical trial	Diet containing 15 ± 8 g/day soy protein and 39 ± 17 mg/day soy isoflavones	Control diet	144	CRP did not change significantly
4.4 Azadbakht, L. 2008 Iran	Type 2 diabetes with nephropathy *N* = 41 F = 23 M = 18	Age: 62.0 ± 12.0 BMI: N/M	Randomized clinical trial	Diet containing 14 ± 8 g/day soy protein and 36 ± 13 mg/day soy isoflavones	Control diet	192	CRP decreased significantly

Table 1 (continued)

Code Author (year) (country)	Subjects	Age and BMI* (mean ± SD)	RCT$^{\Delta}$	Intervention	Placebo	Duration (week)	Results
5.1 Bakhtiari, A 2019 Iran	Older women with metabolic syndrome *N* = 75	Age: 63.8 ± 2.82 BMI: N/M	Randomized, single-blind, controlled clinical trial	35 g/day roasted soy-nut (containing 92.5 mg isoflavines and 13.8 gr protein)	Nothing	12	CRP did not change significantly
5.2 Bakhtiari, A 2019 Iran	Older women with metabolic syndrome *N* = 75	Age: 63.8 ± 2.82 BMI: N/M	Randomized, single-blind, controlled clinical trial	35 g/day textured soy protein (containing 117.2 mg isoflavines and 18.2 gr protein)	Nothing	12	CRP did not change significantly
6 Eslami, O. 2019 Iran	Patients with nonalcoholic fatty liver disease *N* = 64 M: 19 F: 45	Age: 46.25 ± 10.51 BMI: 30.90 ± 3.62	Randomized Clinical Trial	Soy milk containing 6.5 gr/day soy protein and 6.2 mg/day isoflavones	Nothing	8	CRP decreased significantly
7 Fanti, P. 2006 USA	ESRD patients with systemic inflammation *N* = 25 M = 21 F = 14	Age: 61.0 ± 14.5 BMI: 28.1 ± 7.5	Randomized, double-blinded, controlled clinical trial	Soy powder containing 30 gr soy protein and 78 mg/day isofavones	Milk powder	8	CRP did not change significantly
8 Hilpert, K. F. 2005 USA	Moderately hypercholesterolemic adults *N* = 32 F:14 M:18	Age: 57.9 ± 0.93 BMI: 26.1 ± 3.11	Randomized cross-over trial	Diets containing 25 g/d soy protein and 90 mg/d isoflavones	Control diet	6	CRP did not change significantly
9.1 Jenkins, D. J 2002 Canada	Postmenopausal women *N* = 18	Age: N/M BMI: N/M	Randomized cross-over trial	Low isoflavones soy protein foods (supplied 10 mg/day isoflavones and 52 g/day soy protein)	Regular diet	4	CRP did not change significantly
9.2 Jenkins, D. J 2002 Canada	Postmenopausal women *N* = 18	Age: N/M BMI: N/M	Randomized cross-over trial	High isoflavones soy protein foods (supplied 73 mg/day isoflavones and 50 g/day soy protein)	Regular diet	4	CRP did not change significantly
9.3 Jenkins, D. J 2002 Canada	Hypercholesterolemic men *N* = 23	Age: N/M BMI: N/M	Randomized cross-over trial	Low isoflavones soy protein foods (supplied 10 mg/day isoflavones and 52 g/day soy protein)	Regular diet	4	CRP did not change significantly
9.4 Jenkins, D. J 2002 Canada	Hypercholesterolemic men *N* = 23	Age: N/M BMI: N/M	Randomized cross-over trial	High isoflavones soy protein foods (supplied 73 mg/day isoflavones and 50 g/day soy protein)	Regular diet	4	CRP did not change significantly

Table 1 (continued)

Code Author (year) (country)	Subjects	Age and BMI* (mean ± SD)	RCT$^{\Delta}$	Intervention	Placebo	Duration (week)	Results
10 Jung, S. M 2023 USA	Adult men or women with hypertention or hyperlipidemia *N* = 27	Age: 51.6 ± 13.5 BMI: 32.3 ± 7.3	Randomized cross-over trial	Fermented soy powder 9.4 gr soy protein plus 36 mg isoflavones	Dried sprouted brown rice	12	CRP did not change significantly
11.1 Kani, A. H. 2017 Iran	Patients with nonalcoholic fatty liver disease *N* = 30 F = 16 M = 14	Age: 49.3 ± 3.5 BMI: N/M	Randomized clinical trial	Low-calorie low carbohydrate diet containing 30 g/day soy nut (supplied 11.3 g/day protein, 102 mg/day phytoesterogen)	Low-calorie diet	8	CRP decreased significantly
11.2 Kani, A. H. 2017 Iran	Patients with nonalcoholic fatty liver disease *N* = 30 F = 16 M = 14	Age: 49.3 ± 3.5 BMI: N/M	Randomized clinical trial	Low-calorie low carbohydrate diet containing 30 g/day soy nut (supplied 11.3 g/day protein, 102 mg/day phytoesterogen)	Low-calorie low carbohydrate	8	CRP decreased significantly
12 Karamali, M. 2018 Iran	Women with polycystic ovary syndrome *N* = 60	Age: 25.0 ± 5.7 BMI: 28.7 ± 6.1	Randomized clinical trial	Diet containing 20 gr/day soy pro and 97.5 mg/day isoflavones	Control diet	8	CRP did not change significantly
13 Liu, Z. M. 2014 Hong Kong	prehypertensive postmenopausal women *N* = 270	Age: 57.6 ± 5.3 BMI: 23.2 ± 3.5	Randomized, double-blind, controlled trial	40 g/day soy flour (containing 12.8 g protein and 49.8 mg total isoflavones (23.2 mg daidzein and 19.4 mg genistein))	40 g low-fat milk powder	24	CRP decreased significantly in intervention group
14.1 Liu, Z. M. 2012 Hong Kong	Prediabetes postmenopausal women *N* = 180	Age: 56.4 ± 4.7 BMI: 24.1 ± 3.8	Randomized, double-blind, controlled trial	15-g/day soy protein and 100-mg isoflavones (35 mg daidzin, 59 mg genistin and 4 mg	15 g/day milk protein	12	CRP did not change significantly
14.2 Liu, Z. M. 2012 Hong Kong	Prediabetes postmenopausal women *N* = 180	Age: 56.4 ± 4.7 BMI: 24.1 ± 3.8	Randomized, double-blind, controlled trial	15-g/day soy protein and 100-mg isoflavones (35 mg daidzin, 59 mg genistin and 4 mg	15 g/day milk protein	24	CRP did not change significantly
15 Liu, Z. M. 2020 Hong Kong	Postmenopausal women with either pre- or stage 1 hypertension	Age: 57.6 ± 5.3 BMI: N/M	Randomized, double-blind, controlled trial	40 g soy flour contained 12.8 g protein and 49.8 mg total isoflavones	40 g low-fat milk powder	24	CRP did not change significantly
16.1 Matthan, N. R. 2007 USA	Hypercholesterolemic subjects *N* = 28 M = 2 F = 26	Age: 65 ± 6 BMI: 27 ± 3	Randomized cross-over design	Diet containing soybean (providing 7.5% of energy soy protein and 66.0 mg/1000 kcal soy isoflavones	Diet containing animal protein	6	CRP did not change significantly

Table 1 (continued)

Code Author (year) (country)	Subjects	Age and BMI* (mean ± SD)	RCT$^{\Delta}$	Intervention	Placebo	Duration (week)	Results
16.2 Matthan, N. R. 2007 USA	Hypercholesterolemic subjects *N* = 28 M = 2 F = 26	Age: 65 ± 6 BMI: 27 ± 3	Randomized cross-over design	Diet containing soy flour (providing 6.8% of energy soy protein and 55.4 mg/1000 kcal soy isoflavones	Diet containing animal protein	6	CRP did not change significantly
16.3 Matthan, N. R. 2007 USA	Hypercholesterolemic subjects *N* = 28 M = 2 F = 26	Age: 65 ± 6 BMI: 27 ± 3	Randomized cross-over design	Diet containing soymilk (providing 7.3% of energy soy protein and 50.8 mg/1000 kcal soy isoflavones	Diet containing animal protein	6	CRP did not change significantly
17 Miraghajani, M. S. 2012 Iran	Type 2 diabetic patients with nephropathy *N* = 25 F = 15 M = 10	Age: 51 ± 10 BMI: 28 ± 4	Randomized, cross-over clinical trial	240 ml/day soy milk (supplied 6.5 gr/day soy protein and 6.2 mg/day isoflavones)	Diary milk	4	CRP did not change significantly
18 Mohammad-Shahi, M. 2016 Iran	Women with rheumatoid arthritis *N* = 25	Age: 45.72 ± 55.45 BMI: 29.62 ± 5.85	Randomized, cross-over clinical trial	Soy milk (supplied 7 g/day soy protein plus 17 mg/day isoflavones)	Dairy milk	4	CRP decrease significantly
19 Nasca, M. M. 2008 USA	Hypertension postmenopausal women *N* = 12	Age: N/M BMI: N/M	Randomized, placebo-controlled, crossover	0.5 cups of soy nuts (containing 25 g soy protein and 101 mg aglycone Isoflavones)	Control diet	8	CRP did not change significantly
20 Nourieh, Z 2012 Iran	Non-menopausal overweight and obese female adults *N* = 24	Age: 37.7 ± 6.36 BMI: 30.85 ± 4.06	Cross-over randomized clinical trial	240 ml/day soy milk (containing 6.5 gr/day soy protein and 6.2 mg/day isoflavones)	Diary milk	4	CRP did not change significantly
21.1 Padhi, E. M. 2015 Canada	Adults with Hypercholesterolemia *N* = 243 M: 89 F: 154	Age: 55.0 ± 8.8 BMI: 28.0 ± 4.6	Randomized, double-blind, placebo-control, clinical trial	Soy muffin containing 25 g/day soy protein and 122 mg/day isoflavones	Wheat muffin	6	CRP did not change significantly
21.2 Padhi, E. M. 2015 Canada	Adults with Hypercholesterolemia *N* = 243 M: 89 F: 154	Age: 55.0 ± 8.8 BMI: 28.0 ± 4.6	Randomized, double-blind, placebo-control, clinical trial	Soy muffin containing 12.5 g/day soy protein and 61 mg/day isoflavones	Wheat muffin	6	CRP did not change significantly
22.1 Rebholz, C. M 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 crossover trial	40 g of soybean protein supplement (supplied 89.3 mg/day isoflavones)	Complex carbohydrate supplements	8	CRP did not change significantly

Table 1 (continued)

Code Author (year) (country)	Subjects	Age and BMI* (mean ± SD)	RCT$^{\Delta}$	Intervention	Placebo	Duration (week)	Results
22.2 Rebholz, C. M 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 crossover trial	40 g of soybean protein supplement (supplied 89.3 mg/day isoflavones)	Milk protein	8	CRP did not change significantly
23 Reverri, E. J. USA 2015	Postmenopausal women and men with cardiometabolic risk *N* = 17 M = 5 F = 12	Age: 56 ± 5 BMI: 31.2 ± 4.0	Randomized, controlled, crossover trial	70 g/day soy nut (supplied 25 g/day protein and 101 mg/day isoflavones)	Control snack	4	CRP did not change significantly
24.1 Richter, C. K. 2017 USA	Adults with moderately elevated blood pressure *N* = 20 M = 9 F = 11	Age: 51.6 ± 29.5 BMI: N/M	Randomized, placebo-controlled, double-blind, three-phase crossover trial	Soy powder Containing 25 g/day soy protein and 42.5 mg/day isoflavones	Control powder	6	CRP did not change significantly
24.2 Richter, C. K. 2017 USA	Adults with moderately elevated blood pressure *N* = 20 M = 9 F = 11	Age: 51.6 ± 29.5 BMI: N/M	Randomized, placebo-controlled, double-blind, three-phase crossover trial	Soy powder Containing 50 g/day soy protein and 85 mg/day isoflavones	Control powder	6	CRP did not change significantly
25 Siefker, K. USA 2006	Hemodialysis Patients *N* = 17 M = 7 F = 10	Age: 27–77 BMI: N/M	Randomized, single-blind, placebo-control, clinical trial	Soy protein powder containing 25 gr/day soy protein and 52 mg/day isoflavones	Whey protein powder	4	CRP did not change significantly
26 Simão, A. N. C. Brazil 2012	Women with the metabolic syndrome *N* = 30	Age: 49·9 ± 11.2 BMI: 37·31 (34·00–46·17)$^{\varphi}$	Randomized clinical trial	29 g/day kinako (containing 12.95 g protein and 50 mg isoflavones)	Nothing	13	CRP did not change significantly
27 van Nielen, M. 2014 Netherlands	Postmenopausal women with abdominal obesity N:15	Age: 61 ± 5 BMI: N/M	Single-blind randomized crossover trial	soy nuts (containing 30 g/d soy protein and 48 mg/d isoflavones)	Meat protein	24	CRP did not change significantly

†: CRP: C-reactive protein

*: BMI: Body Mass Index

‡: N/M: Not mention

Δ: RCT: Randomized clinical trial

Φ: means (95% confidence interval)

the type of chronic diseases in the studied subjects, four studies were performed on participants with metabolic syndrome [24, 39, 40, 55], three studies on patients with overweight or obesity [38, 47, 51], six studies on patients with hypertension [46, 48, 50, 57–59] four studies on patients with renal diseases [25, 41, 45, 53], two studies on patients with nonalcoholic fatty liver disease [26, 27], four studies on hypercholesterolemia patients [42, 44, 52, 54], one study on prediabetic patients [56], one study on participants with cardio-metabolic risk factors [49], one study on women with polycystic ovary syndrome [43], and one study on women with rheumatoid arthritis [28].

Quality assessment

Among twenty-seven studies, 10 studies were scored as "good" [26, 40, 43, 48, 50, 51, 54, 56–58], 11 studies as "fair" [24, 25, 27, 39, 41, 46, 47, 52, 53, 55, 59] and 6 studies as "weak" [28, 38, 42, 44, 45, 49] according to Cochrane guidelines. Allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome, and selective reporting were the sources of high risk of bias in nine [27, 38, 41, 42, 44, 46, 47, 52, 59], seventeen [24–28, 38–40, 42–47, 49, 52, 55], ten [25, 28, 38, 42, 44, 46, 47, 49, 52, 58], eight [26, 38, 41, 47, 50, 53, 54, 59], and two [45, 49] studies, respectively. Random sequencing were low in twelve [26, 40, 43, 47, 48, 50–52, 54, 56–58] and unclear in fifteen [24, 25, 27, 28, 38, 39, 41, 42, 44–46, 49, 53, 55, 59] studies. Further details about the quality assessment of included studies are presented in Table 2.

Pooled estimate, subgroup analysis, meta-regression analysis, sensitivity analysis, and publication bias

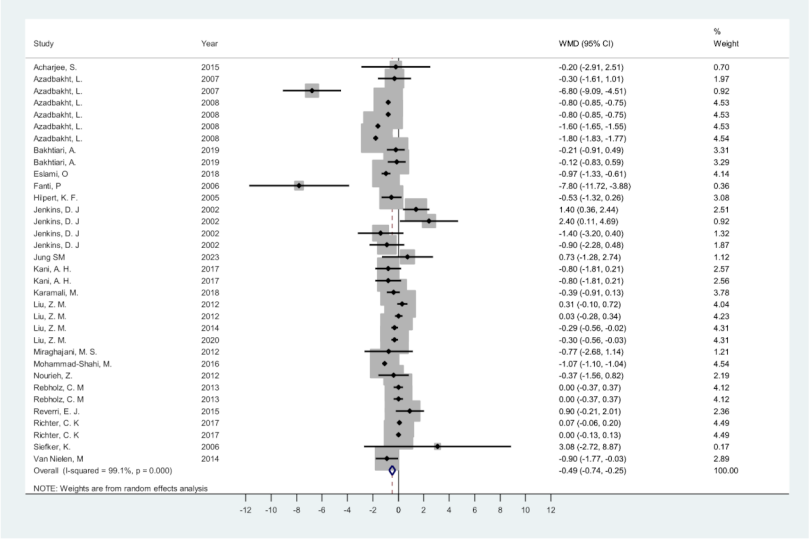
The effect of soy isoflavones containing protein on serum concentration of CRP was assessed in twenty-two studies with thirty-four effect sizes. The overall effect of soy isoflavones containing protein on serum CRP is represented in Fig. 2A. The overall estimates demonstrated that this combination significantly reduced serum levels of CRP in comparison with control group (weighted mean difference (WMD)= -0.49 mg/L 95% CI: -0.74, -0.25; $P<0.001$) with high heterogeneity ($I^2=99.1\%$, Cochrane's Q test,

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

Author name, publication year	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
Anderson, 2007	U	H	H	H	H	U	Weak
Azadbakht, 2007	U	U	H	U	L	L	Fair
Azadbakht, 2008	U	U	H	H	L	L	Fair
Bakhtiari, 2019	L	L	H	L	L	L	Good
Eslami, 2018	L	L	H	L	H	U	Good
Fanti, 2006	U	H	L	L	H	U	Fair
Hilpert, 2005	L	H	H	H	L	U	Fair
Jenkins, 2002	U	H	H	H	L	U	Week
Jung, S. M, 2023	U	H	L	L	H	U	Fair
Kani, 2017	U	H	H	L	L	U	Fair
Karamali, 2018	L	U	H	L	L	U	Good
Liu, 2014	L	L	L	L	L	L	Good
Liu, 2012	L	U	L	L	L	L	Good
Liu, 2020	L	L	L	H	L	U	Good
Matthan, 2007	U	H	H	H	U	U	Weak
Miraghajani, 2012	U	U	H	U	L	H	Week
Mohammad-Shahi, 2016	U	U	H	H	L	U	Week
Nasca, 2008	U	H	H	H	L	L	Fair
Nourieh, 2012	L	H	H	H	H	L	Fair
Padhi, 2015	L	L	L	U	H	U	Good
Rebholz, 2013	L	U	L	L	U	L	Good
Reverri, 2015	U	U	H	H	L	H	Week
Richter, 2017	L	U	L	U	H	L	Good
Siefker, 2006	U	U	L	U	H	L	Fair
Simão, 2012	U	U	H	U	L	L	Fair
van Nielen, 2014	L	U	L	L	L	L	Good

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

A:



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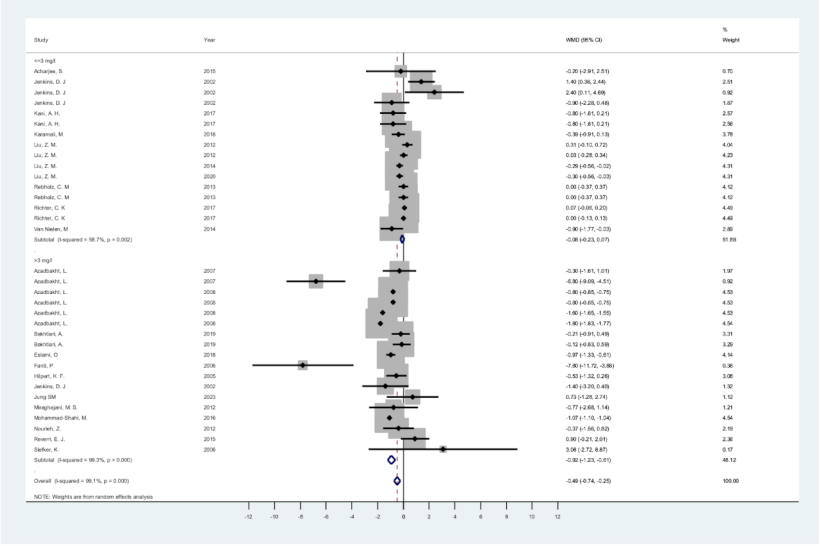

Fig. 2 **A**: Forest plot of the effect of soy isoflavones plus soy protein consumption on serum CRP concentrations. **B**: Forest plot of the effect of soy isoflavones plus soy protein on serum CRP concentrations in subgroup analysis based on baseline CRP concentrations

$P < 0.001$). The results of subgroup analysis revealed that this combination might decrease CRP level only in the studies with isoflavone dose ≤ 63 mg/day (WMD= -0.63 mg/L 95% CI: -0.94, -0.32; $P < 0.001$, $I^2 = 99.5\%$), parallel design (WMD= -0.67 mg/L 95% CI: -1.00, -0.34; $P < 0.001$, $I^2 = 99.4\%$), baseline CRP˃ 3 mg/L (WMD= -0.92 mg/L 95% CI: -1.23, -0.61; $P < 0.001$, $I^2 = 99.3\%$), fair quality (WMD= -1.11 mg/L; 95% CI: -1.52, -0.71; P˂0.001, $I^2 = 99.4\%$), publication year ≤ 2013 (WMD= -0.62 mg/L; 95% CI: -0.97, -0.27; P˂0.001, $I^2 = 99.2\%$) participants with age ˃ 57 years old (WMD= -0.68 mg/L; 95% CI: -1.03, -0.32; $P < 0.001$, $I^2 = 99.4\%$), unknown BMI (WMD= -0.83 mg/L; 95% CI: -1.26, -0.40; $P < 0.001$, $I^2 = 99.6\%$), both sex (WMD= -0.61 mg/L; 95% CI: -0.98, -0.24; $P = 0.001$, $I^2 = 99.5\%$), and studies conducted in Asia (WMD= -0.72 mg/L; 95% CI: -0.99, -0.45; P˂0.001, $I^2 = 99.3$) (Table 3**&** Fig. 2B). As shown in Table 3, subgroup analysis based on different studied variables could not reduce the heterogeneity between studies except sex. The results of univariate meta-regression analysis are represented in Table 4; Fig. 3. The results did not present any significant effect of higher dose of soy isoflavones on studied effect size (Coefficient = 0.0006; 95% CI: -0.012, 0.013; $P = 0.925$) even after adjustment for other variables (Coefficient= -0.003, 95% CI: -0.015, 0.010; $P = 0.672$). Other studied variables also did not have any

Table 3 Results of subgroup analyses for studies evaluating the effect of soy isoflavones plus soy protein on serum concentration of CRP

	Subgroup	No. of trial	Change in CRP (95% CI)	*P*-value	I^2 (%)	$P_{heterogeneity}$
Total	-	34	-0.49 (-0.74, -0.25)	< 0.001	99.1	< 0.001
Isoflavones dose (mg)	≤ 63 mg/d	17	-0.63 (-0.94, -0.32)	< 0.001	99.5	< 0.001
	> 63 mg/d	17	-0.28 (-0.58, 0.01)	0.06	75.8	< 0.001
Trial Design	Parallel	16	-0.67 (-1.00, -0.34)	0 < 0.001	99.4	< 0.001
	Cross-over	18	-0.30 (-0.75, 0.15)	0.188	97.2	< 0.001
Intervention duration	≤ 56 day	23	-0.43 (-0.86, -0.08)	0.017	96.5	< 0.001
	> 56 day	11	-0.56 (-0.94, -0.19)	0.003	99.6	< 0.001
Baseline CRP (mg/l)	≤ 3 mg/l	16	0.08 (-0.23, 0.07)	0.316	58.7	0.002
	> 3 mg/l	18	-0.92 (-1.23, -0.61)	< 0.001	99.3	< 0.001
Sample size	≤ 45	17	-0.51 (-0.92, -0.11)	0.012	99.5	< 0.001
	> 45	17	-0.47 (-0.83, -0.12)	0.009	93.7	< 0.001
Geographical Region	Americas	13	0.04 (-0.21, 0.30)	0.740	67.4	< 0.001
	Europe	1	-0.90 (-1.77, -0.03)	0.042	-	-
	Asia	20	-0.72 (-0.99, -0.45)	< 0.001	99.3	0.001
Age	≤ 57 year	17	-0.21 (-0.62, 0.20)	0.314	97.5	< 0.001
	> 57 year	15	-0.68 (-1.03, -0.32)	< 0.001	99.4	< 0.001
	Unknown	2	-3.48 (-9.85, 2.89)	0.284	95.7	< 0.001
Sex	Female	15	-0.31 (-0.74, 0.12)	0.154	93.7	< 0.001
	Male	2	-1.8 (-2.18, 0.01)	0.052	0	0.666
	Both	17	-0.61 (-0.98, -0.24)	0.001	99.5	< 0.001
BMI	≤ 28	13	-0.26 (-0.71, 0.19)	0.252	79.1	< 0.001
	> 28	9	-0.30 (-0.79, 0.18)	0.221	90.7	< 0.001
	unknown	12	-0.83 (-1.26, -0.40)	< 0.001	99.6	< 0.001
	Good	13	-0.16 (-0.33, 0.003)	0.054	73.2	< 0.001
Quality assessment	Fair	14	-1.11 (-1.52, -0.71)	< 0.001	99.4	< 0.001
	Weak	7	0.02 (-1.06, 1.09)	0.978	86	< 0.001
Publication year of article	≤ 2013	19	-0.62 (-0.97, -0.27)	< 0.001	99.2	< 0.001
	> 2013	15	-0.35 (-0.75, 0.05)	0.085	97.5	< 0.001

CRP: C-reactive protein, BMI: body Mass index, mg: milligram, mg/l: milligram per liter, mg/d: milligram per day, CI: confidence interval

Table 4 Univariate meta-regression analysis of the association of intervention or participant characteristics with the effect size (effect of soy isoflavones plus soy protein on serum CRP) in chronic inflammatory diseases

	No. of trial	Coefficient (95% CI)	*P*-value
Isoflavones dose (mg)	34	0.0006 (-0.012, 0.013)	0.925
Protein dose (g)	34	0.68 (-0.12, 1.47)	0.092
Trial design	34	-0.38 (-0.45, 1.20)	0.362
Intervention duration	34	-0.05 (-0.92, 0.83)	0.913
Baseline CRP (mg/l)	34	-0.82 (-1.50, -0.14)	0.020
Sample size	34	-0.04 (-0.90, 0.83)	0.927
Geographical region	34	-0.38 (-0.79, 0.02)	0.062
Age	32	-0.43 (-1.07, 0.21)	0.181
Sex	34	-0.14 (-0.57, 0.29)	0.506
BMI	22	0.09 (-1.08, 1.25)	0.876
Quality assessment	34	-0.13 (-0.70, 0.44)	0.650
Study publication year	34	0.30 (-0.55, 1.15)	0.473

CRP: C-reactive protein, BMI: body Mass index, mg: milligram, mg/l: milligram per liter, CI: confidence interval, g: gram

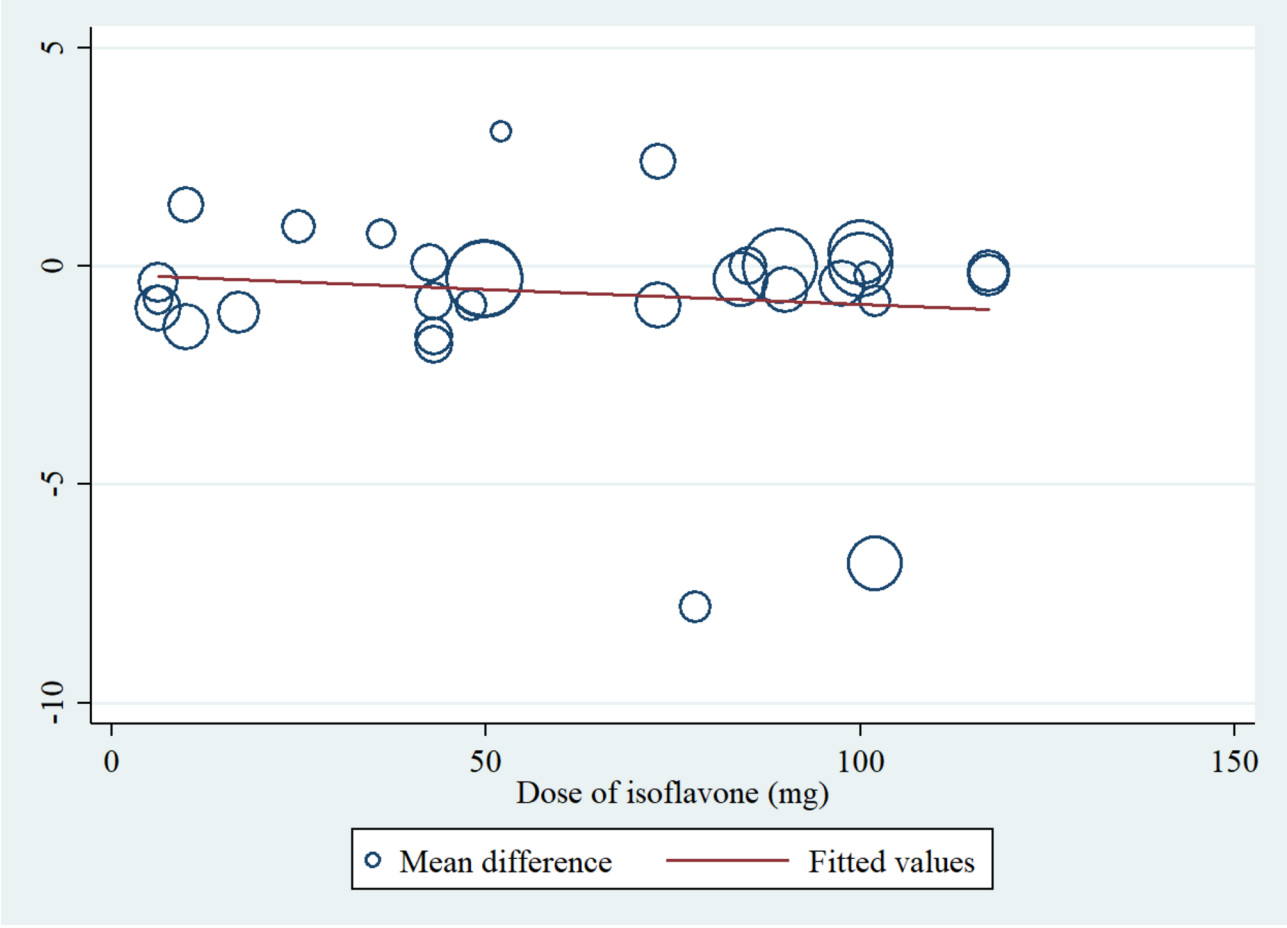

Fig. 3 Meta-regression plot of the effect of soy isoflavones dose on soy isoflavones plus soy protein effect on CRP (dose-response analysis). Values are in mg/L

significant relationship with effect size of this combination on CRP levels in univariate meta-regression analysis except baseline CRP levels (Table 4). The funnel plot was not visually symmetric (Fig. 4) and the Egger and Begg tests also displayed evidence of publication bias (Egger test *P*-value < 0.001; Begg test *P*-value = 0.027). Sensitivity analysis indicated that the overall effect was not significantly changed by excluding each study (Fig. 5).

Discussion

The present study is the first review article that has explained the effect of soy isoflavones containing protein on CRP levels in various subgroups among participants with chronic inflammatory diseases. We included twenty-seven and twenty-two papers in our systematic review and meta-analysis, respectively. According to our meta-analysis results based on 34 data points, soy isoflavones containing protein could significantly decrease serum levels of CRP. In our previous study, we showed that soy isoflavones could not decrease serum concentration of CRP among participants with chronic inflammatory diseases [60] while our study revealed that soy isoflavones in combination with soy protein could reduce serum concentration of CRP among this population. Although our meta-analysis results showed a significant reduction in serum levels of CRP, the extent of this reduction may not hold clinical significance.

The results of our subgroup analysis have shown that soy isoflavones containing protein are more effective in participants aged˃57 compared with ≤57. Since the results of clinical and preclinical studies have shown the anti-inflammatory effects for estrogen [61], we suggest that the anti-inflammatory effects of phytoestrogens in old subjects with low sex hormone levels are much stronger than in young subjects. It might be also possible that phytoestrogen is ineffective in subjects with high endogenous estrogen, or they may compete for binding to receptors. Therefore, soy isoflavones in combination with protein might be less effective in young participants.

Likewise, we found that the combination of soy isoflavones containing protein could decrease CRP in Asian population, but not in Americans. One reason for this result might be the participants' ability for producing equol from one of soy isoflavones called daidzein.

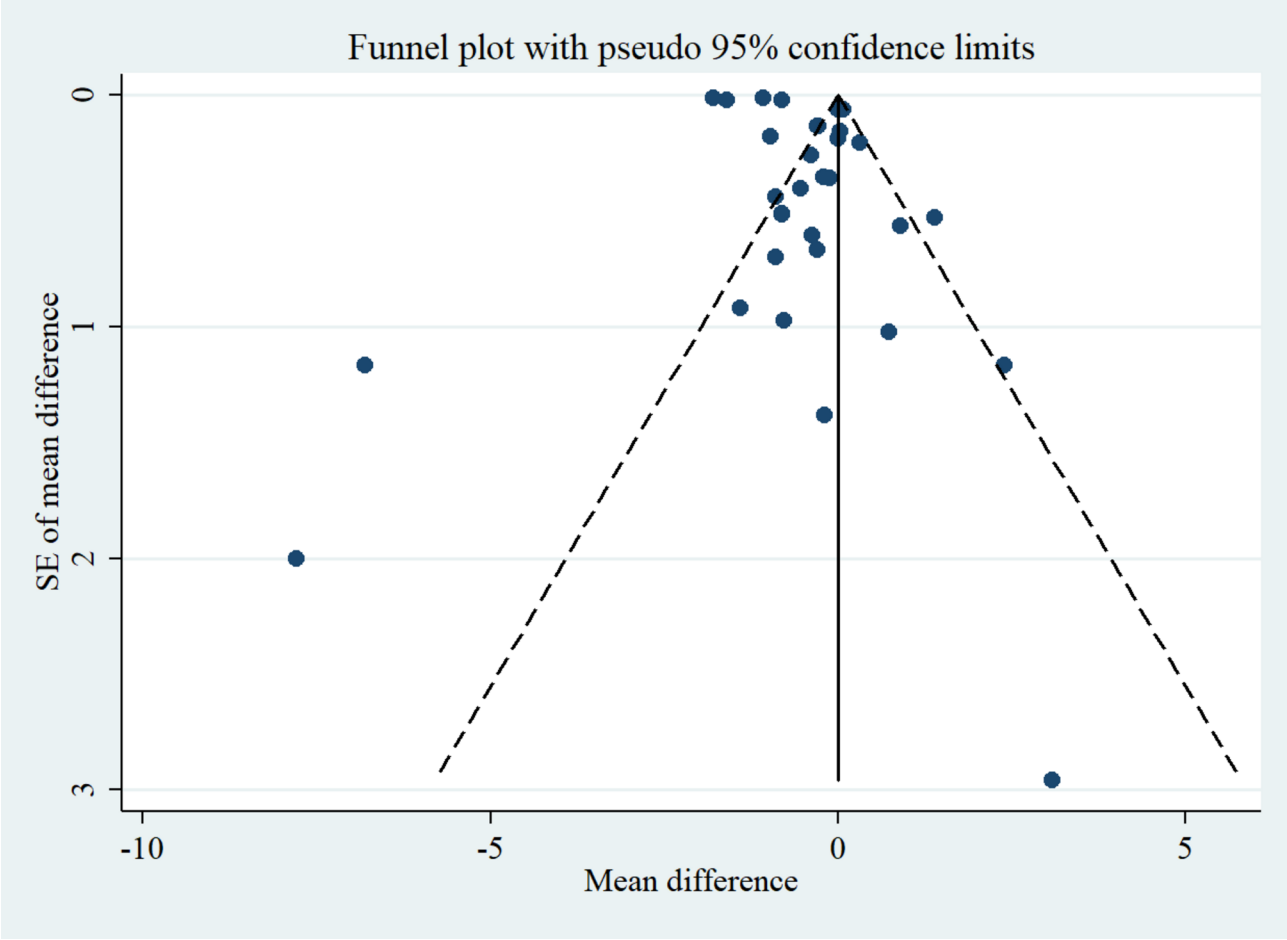

Fig. 4 Funnel plots for the studies of the effects of soy isoflavones plus soy protein consumption on serum CRP concentrations

Compared to the other isoflavones, equol has stronger antioxidant activity. According to the scientists, one reason for anti-inflammatory effects of soy isoflavones might be anti-oxidant effects of these ingredients. Evidence has indicated that the ability for equal production among American adults is less than Asian adults [62]. Therefore, non-significant result among American people in this article might be due to their inability in equol production.

New evidence has repeatedly proposed that the subjects with higher levels of inflammatory mediators might most likely benefit from intervention compared with subjects with lower inflammatory mediators [63]. Having confirmed this suggestion, we found a greater lowering-effect of soy isoflavones containing protein in the population with higher baseline levels of CRP.

Our meta-analysis results confirmed a substantial heterogeneity among RCTs that were included in our study even in the most subgroup analyses. Probable reasons for this heterogeneity might be different participants' ethnic diversity, participants' characteristics such as lifestyle, participants' ability in isoflavones metabolization, intervention methods, and participants' systemic inflammation that change the serum levels of inflammatory mediators.

This study has several limitations that need to be considered when interpreting the results. No data was provided about drug use during the study period that could affect inflammatory markers. Although confounding effects of medicine usage cause difficulty in reaching conclusions [64], we conducted subgroup analysis based on current health status to reduce confounding effects of medicine. Another concern is the variety of sources of isoflavones and protein in the trials. Since the available evidence was limited, we could not exclude the confounding effect of the different sources of isoflavones and protein on treatment effects; however, we reported the results in systematic review and compared their results in Table 1. Furthermore, the different effects of soy isoflavones containing protein on serum CRP levels among males and females might also be interesting. Only one study with two effect sizes evaluated the effect of this combination on males; therefore, the firm results regarding the difference between genders about the magnitude of this intervention could not be addressed in the current

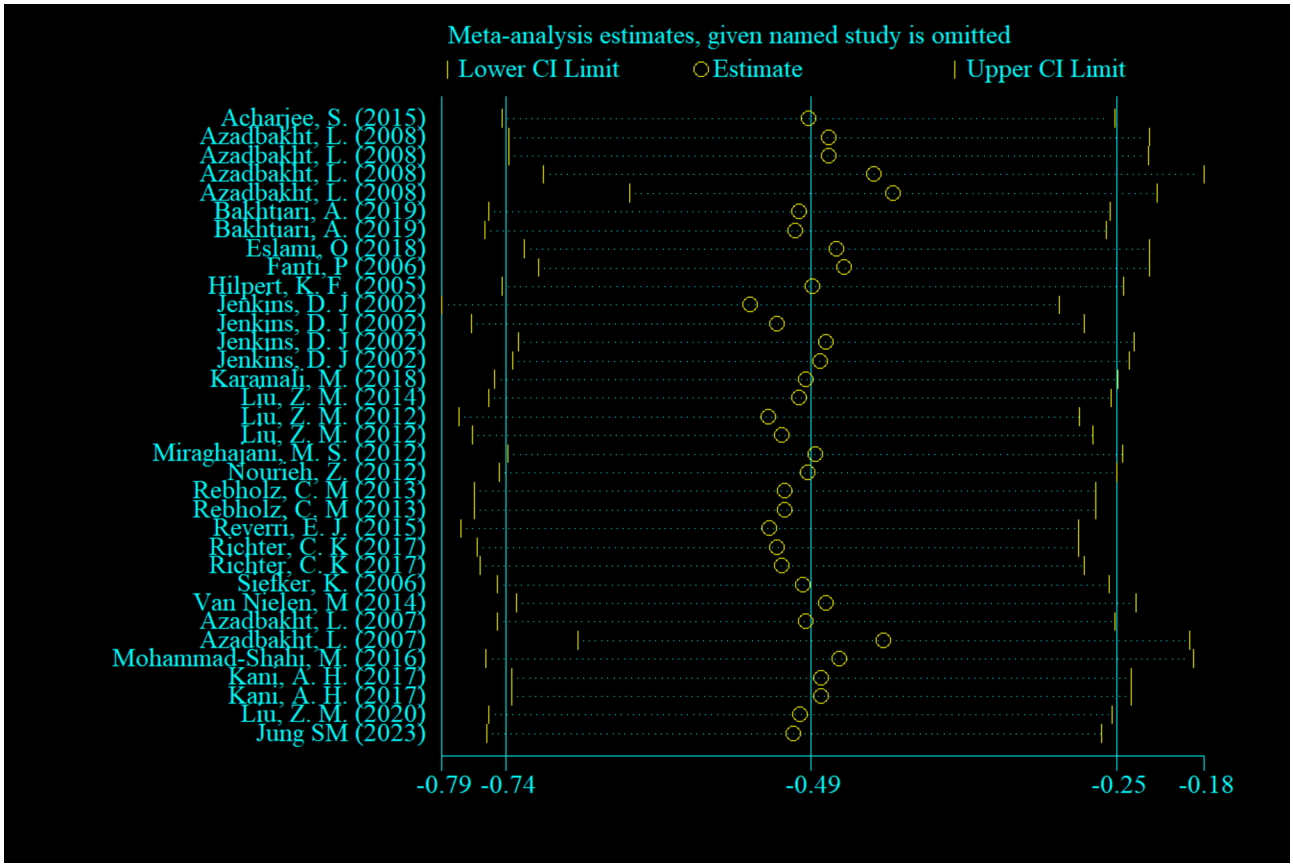

Fig. 5 Sensitivity analysis (leave-one out method)

analysis. In addition, we excluded three articles with a very large effect sizes from our analysis [38, 54, 55]; however, the details of these studies were documented, and their results were included in Table 1. Additionally, we performed the meta-analysis both with and without these studies, but their exclusion did not change our overall findings. There was also significant heterogeneity in our analysis even in most subgroup analyses. Finally, most of the included trials in meta-analysis did not measure serum or urine levels of isoflavones. Therefore, isoflavones bioavailability and dietary compliance were not affirmed. To minimize the impact of this confounding factor, we conducted a dose-response analysis.

The present study also has its strengths. The most important strength of this study is that, to our knowledge, it is the first meta-analysis to assess the effects of soy isoflavones containing protein in participants with chronic inflammatory diseases. Furthermore, we included data derived from several RCTs in our meta-analysis that diminished the chances of bias. In addition, the main strength of this paper is that the subjects who participated in the trials did not take any other food supplements that could change the effect of soy isoflavones containing protein administration. Furthermore, intervention benefits can vary depending on the subjects' health condition, so conducting this study exclusively on participants with chronic inflammatory diseases is a strong point of our study.

Conclusion

Our result clearly showed that soy isoflavones combined with soy protein had a beneficial effect on inflammation in participants with chronic inflammatory disease. Supplementation may be more effective in subjects aged ˃57, CRP levels ˃3 mg/L, and studies conducted in Asia. However, since there was high heterogeneity across studies, our results need to be interpreted with caution. More large-scale and high quality interventional studies will be needed to clarify the current results.

Abbreviations

BMI	Body mass index
CI	Confidence interval
CRP	C-reactive protein
CVDs	Cardiovascular diseases
HTN	Hypertension
IL-6	Interleukin-6
MDs	Mean differences
Mets	Metabolic syndrome
NF-κB	Nuclear factor-κB
NO	Nitric oxide
RCTs	Randomized clinical trials
ROS	Reactive oxygen species

SD Standard deviation
SE Standard error
TNF-α Tumor necrosis factor-alpha
T2DM Type 2 diabetic mellitus
WMD Weighted mean difference

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s41043-025-00902-6.

Supplementary Material 1

Supplementary Material 2

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Author contributions
The design of search strategy was done by AGh. MH and AGh performed the systematic search and finding relevant RCTs. Data extraction was performed by MH and BA. AGh performed statistical analysis. The manuscript was written by All authors. All discrepancies in every stage were solved through group discussions.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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