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Soy Supplementation Does Not Affect Serum Adiponectin Levels in Adults: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

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The authors declare that they have no competing interests.

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ABSTRACT

Numerous studies have indicated that low levels of serum adiponectin are linked with the development of various chronic diseases. While some recent research has suggested that soy has a positive impact on serum adiponectin levels, the results are inconsistent. Therefore, we aim to conduct a thorough systematic review and meta-analysis of randomized controlled trials (RCTs) that investigate the effects of soy on serum adiponectin levels in adults. The search was conducted until March 2024 on PubMed, Scopus, Web of Science, and Cochrane Library databases to identify RCTs that studied the effects of soy supplementation on serum adiponectin levels. A random-effects model was used to pool the weighted mean differences (WMDs). Ten and nine RCTs were selected for the systematic review and meta-analysis, respectively. After analyzing data from 9 eligible RCTs, it was found that soy supplementation did not significantly impact the concentrations of adiponectin (WMD = −0.24 μg/mL; 95% confidence interval, −1.56 to 1.09; p = 0.72). However, there was significant heterogeneity between the studies (I^2 = 89.8%, p < 0.001). Sensitivity analysis showed that overall estimates were not affected by the elimination of any study. We did not observe any evidence regarding publication bias. In conclusion, soy supplementation did not have a significant effect on adiponectin levels in adults. However, further RCTs are needed with longer intervention duration, higher doses, and studies conducted in different countries.

Keywords: Soy foods; Adiponectin; Soy protein; Systematic review; Meta-analysis

INTRODUCTION

Adiponectin is a pleiotropic hormone exclusively secreted by adipocytes and has important anti-inflammatory, anti-atherosclerotic, and anti-obesity effects [1,2]. It is also an insulin-sensitizing hormone, which plays a pivotal role in the regulation of energy homeostasis, inflammation, and cell proliferation [2,3]. Previous investigations have suggested that the low serum adiponectin concentration was associated with the incidence of various chronic diseases such as cardiovascular diseases (CVDs), diabetes, cancers, and chronic kidney disease [3-5]. Adiponectin levels in humans can be increased through indirect methods such as weight loss or physical activity [6,7]. Therefore, improving the level of adiponectin is one of the important goals of health systems. Several studies have investigated the impact of

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pharmacological interventions and surgery on adiponectin levels [8,9]. In recent years, the effect of various dietary factors on improving the level of this hormone has been investigated [10-12]. One such dietary component is soy foods.

Soy foods are commonly consumed in Asian diets but are less frequently consumed in Western diets [13,14]. Soy foods are rich in soluble fibers, plant protein, polyunsaturated fat, isoflavones, vitamins, and minerals combined with a low glycemic index [15,16]. Previous studies have found that consuming soy protein or isoflavones is linked to a lower risk of CVD risk factors, including hypertension, inflammation, obesity, blood lipid profile, glycemic control, and endothelial function [17-20]. Recently, lots of clinical trials have investigated the effects of soy and soy products on serum levels of adipokines, and have reported mixed findings [21-30]. The variability in study results may be due to differences in design, individual characteristics, soy dose, and supplemental duration. In addition, various meta-analyses in this field have produced differing results [31-34]. Therefore, we conducted a meta-analysis of randomized controlled trials (RCTs) to quantify the effects of soy on serum adiponectin levels in adults.

MATERIALS AND METHODS

The study was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline [35]. This review protocol was not published.

Search strategy

PubMed, Scopus, Web of Science, and Cochrane Library databases were systematically searched for articles published in English up to 30 March 2024, with no start-date restriction. In brief, search terms included: (soy OR tofu OR soybeans OR soymilk OR genistein OR daidzein OR isoflavone OR phytoestrogens) AND (adipokines OR adipocytokines OR adiponectin) AND (intervention OR "intervention study" OR "controlled trial" OR randomised OR randomised OR random OR randomly OR placebo OR assignment OR "clinical trial" OR trial OR assignment OR "randomised controlled trial" OR "randomised clinical trial" OR RCT OR blinded OR "double-blind" OR "double-blinded" OR trial OR "clinical trial" OR trials OR "Cross-Over Studies" OR "Cross-Over" OR "Cross-Over Study" OR parallel OR "parallel study" OR "parallel trial"). In addition, we manually checked all reference lists of the included articles and related reviews to ensure no relevant studies were overlooked.

Including and excluding criteria

Two investigators (J.K. and P.Sh.) independently reviewed all potentially relevant articles, and disagreement was resolved by discussion. The inclusion criteria of the study were as follows: 1) RCTs that were conducted on adults (participants ≥ 18 years old), and 2) RCTs that provided sufficient data on the baseline and final measures of adiponectin in both soy and control groups. The exclusion criteria of the study were as follows: 1) RCTs with an intervention duration of less than 2 weeks, 2) studies that investigated the effect of soy in combination with other plants, 3) studies that were not RCTs, and 3) RCTs that did not provide sufficient information regarding the outcome measures in the soy or control groups. If study populations were reported more than once, we used the result with a longer follow-up time.

Data extraction and quality assessment

The following information was extricated from each article: name of first author; year of publication; study design, location of study, total sample size, study duration, mean age,

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body mass index (BMI) and sex of participants, type of intervention and control, health status of the participants, and mean and standard deviation (SD) of outcome measures at the baseline and the final stage of the study. Two investigators (J.K. and P.Sh.) individually extracted the data using a standard extraction form. In cases where required data was not available in the published article or could not be extracted from figures, the corresponding author was contacted. The Cochrane Collaboration's tool [36], assesses the quality of RCTs based on random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other sources of bias, was used by two authors for evaluating the study quality independently. For each criterion, the studies were either judged as meeting (low risk of bias), unclear risk of bias, or not meeting (high risk of bias) the criteria based on predetermined guidelines. Disagreements regarding data extraction and quality assessment were settled as described above.

Statistical analysis

The mean change value for adiponectin with their SDs was extracted from individual studies to calculate the weighted mean difference (WMD) and its standard errors between the soy and control groups, to be used as the effect size for favorable outcomes. The effect size was pooled using a random-effects model in conjunction with the DerSimonian and Laird method [37]. Possible heterogeneity between studies and the percentage heterogeneity was calculated by using I^2 test, with values of 25%, 50%, and 75% regarded as a low, moderate, and high degree of heterogeneity, respectively [38]. Subgroup analyses were conducted to investigate possible sources of heterogeneity based on intervention duration, study design, and baseline BMI. To evaluate whether the overall effect was steady, sensitivity analysis was performed by deleting one trail at a time, and the effect size was re-calculated. Publication bias was assessed using Egger's [39] regression test. All statistical analyses were conducted using STATA, version 11.2 (Stata Corp, College Station, TX, USA). The p values less than 0.05 were considered statistically significant.

RESULTS

Search results

The search strategy retrieved 390 citations. After the removal of 104 duplicates, titles and abstracts of 286 references were screened. At this stage, 15 full-text articles were judged to be potentially relevant, of which 10 articles [21-30] satisfied the review eligibility criteria. The study selection flow diagram is presented in **Figure 1**.

Characteristics of included studies

Included RCTs had small sample sizes (n = 25–183) and were conducted in the USA, Iran, England, Canada, Spain, and Brazil. Except for three studies, the remaining studies had a parallel design. The intervention period range was 4-96 weeks. The mean age of the included participants was 53 years. Six studies were conducted in post-menopausal women, one in subjects with metabolic syndrome, one in subjects with prostate cancer, one in hypertensive individuals, and one in subjects with rheumatoid arthritis. Detailed information on the included studies is summarized in **Table 1**. The details related to the quality assessment of the studies using the Cochrane collaborations tool are reported in **Table 2**.

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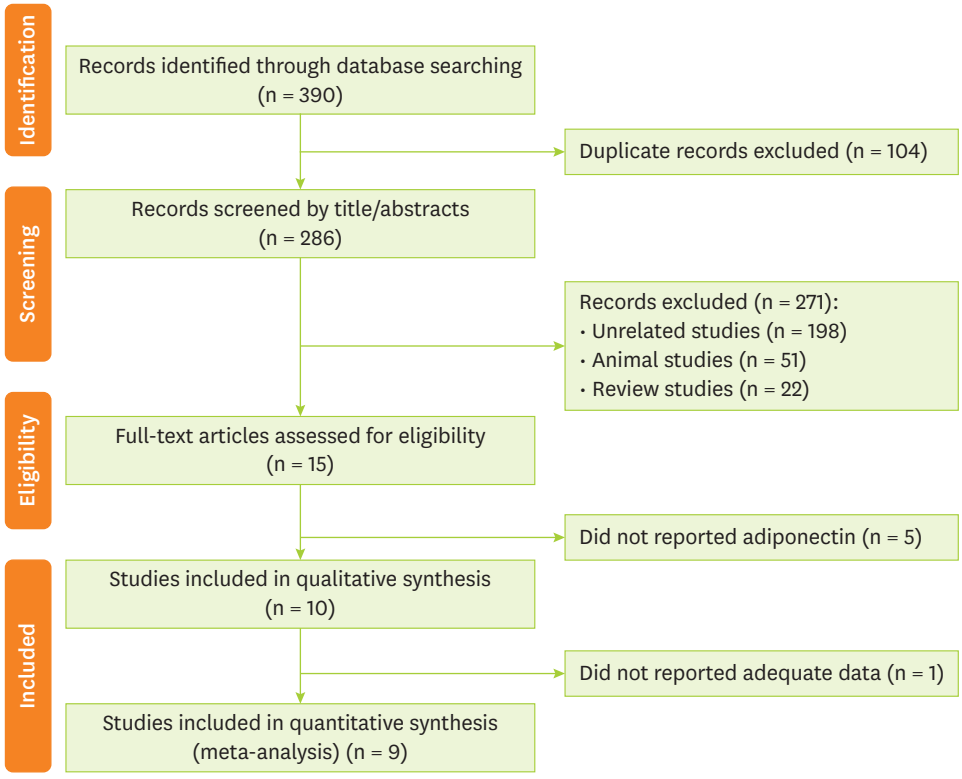

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) flow chart of the study selection process.

Table 1. Characteristics of the studies included in the meta-analysis

Study (publication year, location)	RCT design	Sex, mean age (yr)	Mean BMI	Total sample size	Duration (wk)	Participants	Intervention	Control
Maskarinec et al. [25] (2009, USA)	Parallel	Female (43)	26	183	96	Post-menopausal women	Soy products	Regular diet
Charles et al. [22] (2009, USA)	Parallel	Female (56)	26	75	12	Post-menopausal women	soy protein powder	Placebo powder
Christie et al. [21] (2010, England)	Parallel	Female (54)	35	33	12	Obese post-menopausal women	Soy shakes	Casein without isoflavones
Napora et al. [24] (2011, USA)	Parallel	Male (69)	28	33	12	Prostate cancer	Soy protein	Whole milk protein
Riesco et al. [28] (2012, Canada)	Parallel	Female (58)	28	55	24	Post-menopausal women	Exercise + soy extract	Placebo + exercise
Llaneza et al. [26] (2011, Spain)	Parallel	Female (56)	34	87	24	Post-menopausal women	Diet + exercise + soy isoflavones extract	Diet + exercise
Lozovoy et al. [27] (2012, Brazil)	Parallel	Female (47)	35	30	12	Metabolic syndrome	Soybean	Usual diet
Rebholz et al. [30] (2013, USA)	Crossover	Both (51)	29	48	8	Hypertensive individuals	Soybean protein	Milk protein
Nadadur et al. [23] (2016, USA)	Parallel	Female (58)	28	37	8	Post-menopausal women	Soy protein	Control diet
Mohammad-Shahi et al. [29] (2016, Iran)	Crossover	Female (45)	29	25	4	Rheumatoid arthritis	Soy milk	Dairy milk

RCT, randomized controlled trial; BMI, body mass index.

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Table 2. Quality assessment of included studies based on Cochrane guidelines

Study	Random sequence generation	Allocation concealment	Blinding of participants, personnel	Blinding of outcome assessment	Incomplete outcome data	Selective outcome reporting	Other sources of bias	Overall quality
Maskarinec et al. [25]	U	U	U	L	L	U	U	Fair
Charles et al. [22]	L	L	L	U	L	L	U	Good
Christie et al. [21]	L	L	L	U	L	H	L	Good
Napora et al. [24]	L	U	L	U	L	U	U	Good
Riesco et al. [28]	U	L	L	U	U	U	U	Fair
Llaneza et al. [26]	L	H	L	L	L	L	U	Good
Lozovoy et al. [27]	U	U	H	U	L	L	U	Fair
Rebholz et al. [30]	L	U	L	L	U	L	U	Good
Nadadur et al. [23]	L	U	L	L	U	L	U	Good
Mohammad-Shahi et al. [29]	U	U	H	H	L	U	L	Fair

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

Findings of the systematic review

One of the included studies [21] did not report enough data for analysis, so this study is only reported as a systematic review. This study found no significant change in adiponectin levels after three months of soy supplementation in women with hypertension compared to the control group.

Findings of the meta-analysis

Nine RCTs [22-30] were carried out to investigate the impact of soy and soy products on the serum concentration of adiponectin. These studies involved a total of 573 participants. The combined results of these studies showed that there was no significant change in the levels of serum adiponectin in the intervention group as compared to the control group (WMD = −0.24 μg/mL; 95% confidence interval, −1.56 to 1.09; p = 0.72). However, there was significant heterogeneity between the studies (I^2 = 89.8%, p < 0.001) (**Figure 2**), and this could not be eliminated by conducting subgroup analyses (**Table 3**). In addition, sensitivity analysis showed that any one specific study did not substantially influence the overall results. No evidence of publication bias was shown for the meta-analysis of the adiponectin (Egger's test, p = 0.95).

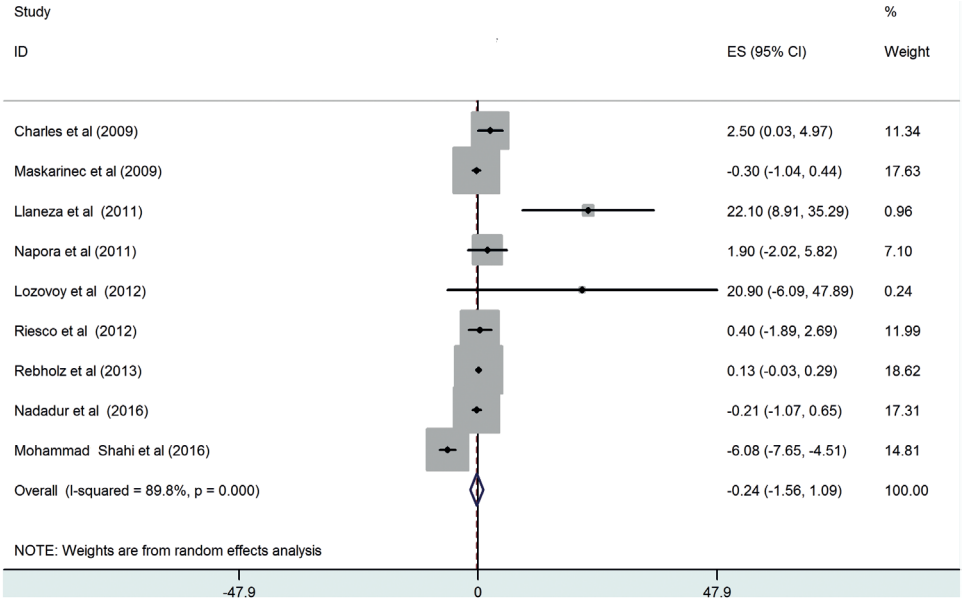

Figure 2. Effect of soy supplementation on serum adiponectin levels.
ES, effect size; CI, confidence interval.

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Table 3. Subgroup analyses to assess the effect of soy supplementation on adiponectin levels

Sub-grouped by	No. of trials	Effect size*	95% CI	I^2 (%)	p for heterogeneity	p for between subgroup heterogeneity
Baseline BMI (kg/m²)						< 0.001
< 30	7	0.08	−0.28 to 0.44	19.5	0.28	
≥ 30	2	21.87	10.02 to 33.72	0.0	0.93	
Duration (wk)						0.90
≤ 8	3	−1.90	−4.36 to 0.56	96.7	< 0.001	
> 8	6	1.75	−0.65 to 4.16	73.1	0.002	
RCT design						0.76
Parallel	7	0.77	−0.61 to 2.15	68.2	0.004	
Crossover	2	−2.92	−9.01 to 3.16	98.3	< 0.001	

CI, confidence interval; RCT, randomized controlled trial; BMI, body mass index.
*Calculated by random-effects model.

DISCUSSION

In the present meta-analysis, we aimed to evaluate the effects of soy supplementation on adiponectin levels in adults. Data analysis showed that soy supplementation had no significant effect on adiponectin. Results of subgroup analysis revealed that subgroup analysis based on trial design, and intervention duration could not change their results. However, when sub-grouped by BMI, the results were significant in obese participants. Due to the limited number of studies in the subsets, interpretation of these results should be done with caution.

The results of the present study are remarkably similar to previous meta-analyses [31,32,34]. The results of these studies indicate that the consumption of soy and its compounds does not have a significant effect on the level of serum adiponectin. However, the results of this study contradict those of a previous meta-analysis [33], which found that soy isoflavones increase adiponectin levels in the postmenopausal women. The reason for the difference observed could be attributed to the various factors. The onset of the postmenopausal period is associated with increased abdominal fat and central obesity, which can lead to metabolic dysfunctions such as insulin resistance, and dyslipidemia, especially when accompanied by visceral fat accumulation. As a result, these individuals have lower levels of adiponectin, making them more susceptible to interventions aimed at increasing their levels [33,40,41].

Although, based on the present results, soy consumption does not have a significant effect on adiponectin levels, some mechanisms have been suggested for the effect of soy on increasing adiponectin levels. Previous studies have shown that soy may reduce obesity markers and thereby increase adiponectin levels [42,43]. It appears that the high sensitivity of adipose tissue to oxidative stress and inflammation leads to a decrease in the gene expression of adiponectin in 3T3-L1 adipocytes when exposed to elevated levels of oxidative stress agents [1,31,44]. Therefore, antioxidant factors such as soy may enhance the secretion of adiponectin from adipose tissue [45]. There is another mechanism that may be linked to the increase in adiponectin, which is the nitric oxide (NO) pathway. Previous studies have found that soy and its products can boost the production of NO in endothelial cells, leading to an increased secretion of adiponectin [31].

Although relatively common side effects were not discussed in any RCT analysis, we cannot neglect allergic reactions caused by soy supplementation. The most common side effects reported after soy intake are digestive upsets, such as constipation and diarrhea. In addition, soy may alter thyroid function in people who are deficient in iodine [46-48].

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Like all reviews, there are some potential limitations in the present study. First, the number of eligible studies in this meta-analysis was relatively small, which may have biased the results to some extent. Second, the high heterogeneity among studies may reduce the validity of the results. Third, in most studies, adiponectin has been reported as a secondary factor and not a primary objective. Fourth, due to the limited number of studies, we were unable to present results for the gender-separated subgroup, which could be a significant factor. In addition, most of the included studies have been done in the USA, which makes it difficult to generalize the results to the rest of the world. None of the included studies measured serum polyphenol content, making it difficult to assess participant compliance. Finally, most studies failed to control for confounders such as diet and physical activity levels, which could impact the results.

In conclusion, we found that soy may not increase adiponectin levels. However, more RCTs with longer intervention duration, higher doses, and studies in different countries are still needed. Furthermore, the confounding effects of diet and physical activity should be adjusted.

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