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The effect of soy consumption on inflammatory biomarkers: A systematic review and meta-analysis of clinical trials

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Abbreviations: IL-6: interleukin 6, TNF-α: tumor necrosis factor α, IL-1β: interleukin 1β, IL-2: interleukin 2, IFN-γ: Interferon γ; MD: mean difference, SD: standard deviation, SE: standard error

Keywords: Soy, Inflammation, Interleukin, Tumor necrosis factor α, Interferon-gamma, Meta-analysis

Disclosure statements:

1   **Abstract**

2   Inflammation is a major cause of chronic diseases. Several studies have investigated the effects

3   of soy intake on inflammatory biomarkers; however, the results are equivocal. The aim of this

4   study was to conduct a systematic review and meta-analysis of clinical trials that evaluated the

5   effect of soy consumption on inflammatory biomarkers. Medline, Scopus, ISI Web of Science,

6   and Google Scholar were systematically searched, up to and including May 2020, for clinical

7   trials that evaluated the effects of soy and soy products on tumor necrosis factor α (TNF-α),

8   Interleukin-6 (IL-6), Interleukin-2 (IL-2), Interleukin1-β (IL1-β), and Interferon gamma (IFN-

9   γ) in adults. A random-effects method was used to calculate overall effects, and subgroup

10   analyses were performed to discern probable sources of inter-study heterogeneity. A total of

11   28 clinical trials were included. Although soy consumption reduced TNF-α (Hedges' g= −0.28;

12   95%CI: −0.49, −0.07), it had no significant effect on IL-6 (Hedges' g= 0.07, 95% CI: −0.14,

13   0.28), IL-2 (MD= −1.38 pg/ml; 95%CI: −3.07, 0.31), IL1-β (MD= −0.02 pg/ml; 95%CI: −0.08,

14   0.03), and IFN-γ (MD= 1685.82 pg/ml; 95%CI: −1604.86, 4976.50). Subgroup analysis

15   illustrated a reduction in TNF-α in in parallel designed studies, at dosages ≥100 mg of

16   isoflavones, and in unhealthy subjects. The present study showed that high doses of isoflavones

17   in unhealthy subjects may yield beneficial effects on TNF-α.

18   **Keywords:** soy, inflammation, interleukin, tumor necrosis factor α, meta-analysis

19   **Introduction:**

20   Inflammation is a complex immune response to the pathogenic agents [1]. Indeed, both cell-

21   mediated and humoral responses are involved in inflammation [2]; whilst reactive oxygen

22   species are key molecules that play a major role in the initiation and progression of the

23   inflammatory response [3].

24   Inflammation may be classified into two types: acute and chronic [4]. Acute inflammation is a

25   short-term immune response to detrimental conditions, such as tissue injury, and can facilitate

26   repair, turnover, and adaptation of tissues [5]. Although chronic inflammation has many

27   characteristics of acute inflammation; it is usually mild and permanent [6]. Although chronic

28   inflammation is not considered as a separate disease, several chronic diseases have an

29   inflammation-based pathogenesis [4]. Accumulating evidence suggests that diabetes [7],

30   cardiovascular diseases [8], cancer [9], obesity [10], rheumatoid arthritis [11], and chronic

31   respiratory diseases [12] are all associated with inflammation.

32   Lifestyle modification, including adopting a healthy diet [13], regular exercise [14], adequate

33   sleep [15], avoiding smoking [16], and stress management [17] can reduce chronic inflammation.

34   Adequate intake of vegetables and legumes are regarded as an important part of a healthy diet

35   [18]. Soybean is a legume, rich in health-promoting components such as vitamin E, vitamin C,

36   folates, thiamin, riboflavin, amino acids, and bioactive compounds [19], whilst, to our

37   knowledge, soybean protein possesses antioxidant, anti-inflammatory, and anticancer

38   properties [20]. In addition to minerals, vitamins, fiber, and omega-3 fatty acids; soybean is

39   considered as a major source of phytoestrogens, particularly isoflavones [21; 22]. Genistein,

40   Daidzein, and Glycitein are the major isoflavones found in soybean [22]. Genistein has anti-

41   inflammatory properties and is a strong inhibitor of tyrosine kinase enzyme [23], leading to, in

42   part, the suggestion that soybean intake may be efficacious in the prevention and treatment of

43   inflammation-based chronic diseases [21].

44   Some studies have reported that soy consumption reduced some inflammatory biomarkers [24;

45   25]; however, equivocally, soy intake had null [26; 27] or unfavorable [28] effects on inflammation

46   in other studies. Therefore, a systematic review and meta-analysis is needed to determine the

47   overall effect of soy consumption on inflammatory biomarkers. Although a previous meta-

48   analysis reported that soy consumption had no significant effect on C-reactive protein (CRP)

49 [29], there is no comprehensive systematic review and meta-analysis of clinical trials that has

50 evaluated the impact of soy intake on other inflammatory markers. Therefore, the purpose of

51 this systematic review and meta-analysis was to determine the effects of soy and soy products

52 on inflammatory biomarkers.

Methods:

54 The present study was conducted according to the Preferred Reporting Items for Systematic

55 Review and Meta-Analysis (PRISMA) [30]. The study protocol was registered on an

56 international prospective register of systematic reviews (PROSPERO) (registration number:

57 CRD42020164481).

Search strategy

59 Electronic databases, including Medline, Scopus, ISI Web of Science and Google Scholar were

60 searched up to and including May 2020. Title, abstract, and keywords of articles were searched

61 using the following keywords: ("soya" or "soy foods" or "soy milk" or "soybeans" or "soybean

62 protein" or " soy" or "isoflavones" or "phytoestrogens" or " genistein" or "genestein" or

63 "glycitein" or " daidzein" or " isolated soy protein" or " textured soy protein") AND

64 ("interleukin-6 " or "IL-6" or "tumor necrosis factor-α" or" TNF-α" or "interleukin" or "

65 interleukin-8" or " inflammation" or "cytokine" or "IL-1β" or "IL-2" or " IL-4" or "IL-8" or

66 "IL-10" or "IFN-γ" or "inflammatory"). The references of the retrieved articles were also

67 searched manually. The search strategy was conducted without any restrictions.

Eligibility criteria

69 Two independent investigators (M.R and F.M) screened title, abstract, and full texts of included

70 articles. All interventions that investigated the effects of soy and soy products on inflammatory

71 biomarkers including tumor necrosis factor α (TNF-α), interleukin-6 (IL-6), interleukin-2 (IL-

72 2), interleukin1-β (IL1-β) or interferon gamma (IFN-γ), in healthy and unhealthy adults, were

73 included. Articles were excluded if they: *1*) were *in vitro* or animal-based studies; *2*) were

74 editorials, letters, review articles, or meeting abstracts; *3*) were short-term (<1 week); *4*) used

75 soy in combination with other foods or adjunct interventions; *5*) had no control group; *6*) did

76 not report dose of soy or isoflavone in intervention group; *7*) reported post-exercise

77 inflammation; *8*) included pregnant women, or children, and *9*) had insufficient reported data.

78 **Data extraction**

79 The following information was extracted from each eligible article: the first author's name and

80 year of publication; sample size; age of participants; design of clinical trial and

81 duration; dosage and type of soy or soy product used in the intervention group; details

82 regarding intervention in control group, and characteristics of subjects. IL-6, TNF-α, IL-2, IL-

83 10, IL-1β, and IFN-γ were considered as main outcomes. Mean and standard deviation (SD) or

84 standard error (SE) for outcomes were extracted. CRP was not entered in the present study

85 because a previous meta-analysis reported the effect of soy consumption on CRP [29].

86 **Assessment of quality**

87 The quality of studies was assessed according to the Cochrane Risk of Bias Tool [31]. Two

88 authors (M.R. and F.M.) independently evaluated the quality of eligible studies through

89 Cochrane Risk of Bias tool including seven domains: *1*) random sequence generation (selection

90 bias), *2*) allocation concealment (selection bias), *3*) blinding of participants and personnel

91 (performance bias), *4*) blinding of outcome assessment (detection bias), *5*) incomplete outcome

92 data (attrition bias), *6*) selective reporting (reporting bias), and *7*) other sources of bias. Each

93 domain was classified into three classes: low risk (one plus (+) sign), high risk (one negative

94 (-) sign), and unclear risk of bias (question mark (?)). Therefore, the overall quality of each

95   study was considered as good (low risk for more than two domains), fair (low risk for two

96   domains), or weak (low risk for less than two domains), respectively.

Statistical analysis

98   This meta-analysis was conducted using STATA software (version 11, Stata Corporation). A

99   limited number of studies reported net change; thus, to calculate effect size in studies that net

100 change was not reported in the soy and control group, we used mean±SD/SE or median and

101 IQR [32; 33]. To compute the overall effect, we converted SE to SD. TNF-α and IL-6 were

102 reported in different units through the studies; therefore, Hedges' g was used for these

103 variables. In contrast, mean difference was applied for IL-1β, IL-2, and IFN-γ. A random-

104 effects model was conducted to calculate pooled effect size for each main outcome. I squared

105 (I^2) and a fixed-effect model were used to evaluate inter-study and between-subgroup

106 heterogeneity, respectively. A pre-planned subgroup analysis based on soy type, soy dosage,

107 duration of intervention, design of the study, gender, age, and health status was performed to

108 discern potential sources of inter-study heterogeneity.

109 To evaluate the possible influence of each study on the pooled effect size, the stability of the

110 results was checked using sensitivity analyses. Egger's regression asymmetry test and Begg's

111 rank-correlation method were conducted to assess publication bias. A P-value <0.05 was

112 considered to represent statistical significance.

Results

Systematic review

115 Details regarding study selection process are illustrated in **Figure 1**. A total of 15179 records

116 were identified through database searching. Subsequently, 3913 duplicate records were

117 removed, and 11266 records were screened. After screening, 11218 records were excluded, and

118   of the 48 articles that remained for full-text assessment, 19 articles were excluded due to being

119   short term (<1 week) trials (n=3), using soy in combination with other intervention (n=5), using

120   gene expression and cell cultures (n=2), reporting limited data regarding amount of pure soy

121   or isoflavones (n=1), reporting post-exercise inflammation (n=1), being meeting abstract (n=1),

122   and having no control group (n=6). Finally, 29 articles were included in qualitative synthesis

123   [24; 25; 26; 27; 28; 34; 35; 36; 37; 38; 39; 40; 41; 42; 43; 44; 45; 46; 47; 48; 49; 50; 51; 52; 53; 54; 55; 56; 57]. Whilst, of 29

124   publications eligible for systematic review, one study was not included in meta-analysis

125   because it did not report applicable data for quantitative analysis, resulting in 28 articles entered

126   into the meta-analysis [57].

127   The result of quality assessment of included articles is shown in **Table 1**. Of 28 included

128   studies, 25 articles were randomized [24; 25; 26; 27; 28; 34; 36; 37; 38; 39; 42; 43; 44; 45; 46; 47; 48; 49; 50; 51; 52; 53;

129   54; 55; 56], and only 16 articles reported randomization methods [24; 25; 26; 27; 28; 34; 36; 37; 38; 39; 44; 45;

130   46; 48; 50; 56]. Fifteen studies were double-blinded [24; 25; 26; 27; 28; 36; 37; 38; 39; 40; 44; 45; 46; 47; 56], and 13

131   trials had no report regarding blinding procedure [34; 35; 41; 42; 43; 48; 49; 50; 51; 52; 53; 54; 55]. Only five

132   articles reported reasons for participant withdrawal [35; 40; 41; 47; 49]. Of the 28 included studies in

133   the meta-analysis, the quality of all articles was high, except for 2 studies which were ranked

134   as low [35; 41].

135   Details of all 28 articles are presented in **Table 2**. Twenty-eight clinical trials that enrolled a

136   total of 1816 participants (mean age=51.4 y) were included in this meta-analysis [24; 25; 26; 27; 28;

137   34; 35; 36; 37; 38; 39; 40; 41; 42; 43; 44; 45; 46; 47; 48; 49; 50; 51; 52; 53; 54; 55; 56]. Unhealthy participants had prostate

138   cancer, metabolic syndrome, irritable bowel syndrome, hypercholesterolemia, rheumatoid

139   arthritis, climacteric syndrome, Hashimoto's thyroiditis, poorly controlled asthma, non-

140   alcoholic fatty liver disease, and hypertension. Soy was used in different forms through the

141   studies, including soy milk, soy protein, soy nut, and isoflavones. The range of dosage of

142   Isoflavones was 40 to 600 mg, whilst the duration of study varied from 4 to 96 weeks. Twenty

143 studies used a parallel design and eight studies used a crossover design. The most reported

144 outcomes were TNF-α (n=22) or IL-6 (n=21), whilst IL-1β and IL-2 were measured in three

145 studies, and IFN-γ level was measured in two studies. IL-10 level was only reported in one

146 study, and therefore, it was only reported in the systematic review.

147 **Meta-analysis**

148 **The effect of soy and soy products on IL-6**

149 A meta-analysis of 21 clinical trials (23 effect sizes) did not yield any significant change in IL-

150 6 level following soy and soy products consumption (Hedges' g: 0.07, 95% CI: –0.14, 0.28)

151 (**Figure 2**). There was significant heterogeneity between trials (I^2=72%; P<0.001); however,

152 we could not discern the sources of heterogeneity by using pre-planned subgroup analysis

153 (**Table 3**).

154 **The effect of soy and soy products on TNF-α**

155 The effect of soy intake on TNF-α level was evaluated in 22 studies (23 effect sizes). Pooled

156 analysis demonstrated a significant reduction in TNF-α in the soy group compared with

157 controls (Hedges' g: –0.28; 95% CI: –0.49, –0.07). A significant inter-study heterogeneity was

158 identified (I^2=82.4%; P<0.001), and pre-planned subgroup analysis by soy dosage, design of

159 the study, health status, and soy type attenuated the heterogeneity (**Figure 3**). As shown in

160 **Figure 3A**, a significant reduction in TNF-α was found in studies that used ≥100 mg of

161 isoflavones (Hedges' g: –0.47; 95% CI: –0.79, –0.14; I^2=58.1%). However, we did not observe

162 any significant effect at dosages <100 mg (Hedges' g: –0.30; 95% CI: –0.73, 0.13; I^2= 89.4%;

163 P for between subgroup heterogeneity=0.007). A significant decrease was shown in parallel

164 designed clinical trials (Hedges' g: –0.35; 95%CI: – 0.66, –0.03; I^2=84.6%); contrastingly,

165 cross-over studies did not show any significant effect (Hedges' g: –0.06; 95% CI: –0.24, 0.13;

166 I^2= 50.0%; P for between subgroup heterogeneity=0.001) (**Figure 3B**). Studies that included

167 unhealthy participants demonstrated a significant reduction in TNF-α (Hedges' g: −0.56;

168 95%CI: −0.97, − 0.14; I^2=90.3%; P for between subgroup heterogeneity=0.005), whilst results

169 in "healthy", "overweight or obese", and "not reported" subgroups were not significant (**Figure**

170 **3C**). Subgroup analysis by soy type further indicated a significant reduction in TNF-α in the

171 studies that used isoflavones supplements (Hedges' g: −1.00; 95%CI: −1.94, −0.06; I^2=94.4%;

172 P for between subgroup heterogeneity <0.001), whilst results in "soy milk", "soy protein", and

173 "soy nut" subgroups were not significant (**Figure 3D**). Further subgroup analyses that could

174 not explain heterogeneity are reported in **Table 3**.

175 **The effect of soy and soy products on IL-2**

176 Overall effect sizes of 3 clinical trials (3 effect sizes) did not show any significant impact of

177 soy consumption on IL-2 level (MD= −1.38 pg/ml; 95% CI: −3.07, 0.31). Although a high inter-

178 study heterogeneity was found (I^2= 99.6%; P<0.001), subgroup analysis was not applicable

179 because of a limited number of studies.

180 **The effect of soy and soy products on IL1-β**

181 Pooled effect sizes of 3 trials (3 effect sizes) did not show any significant effect of soy

182 consumption on IL1-β (MD= −0.02 pg/ml; 95%CI: −0.08, 0.03). There was no heterogeneity

183 between studies (I^2= 0.0%; P=0.447).

184 **The effect of soy and soy products on IFN-γ**

185 Overall effect sizes of 2 trials (2 effect sizes) did not show a significant effect of soy

186 consumption on IFN-γ level (MD= 1685.82 pg/ml; 95%CI: −1604.86, 4976.50). A high inter-

187 study heterogeneity was found (I^2= 99.8%; P<0.001), but subgroup analysis was not carried

188 out because of an insufficient number of studies.

189 **Sensitivity analysis**

190   To evaluate the influence of any individual study on the overall effect size, a sensitivity analysis

191   was Performed. For IL-6, TNF-α, IL-2, and IL-1β, excluding any of the studies did not

192   significantly alter the findings. Furthermore, because of the low number of articles, a sensitivity

193   analysis was not carried out for IFN-γ.

194   **Publication bias**

195   Clinical trials did not show publication bias for IL-6 (P=0.39 for Begg's test; P=0.40 for Egger's

196   test), TNF-α (P=0.27 for Begg's test; P=0.09 for Egger's test), IL-2 (P=0.11 for Begg's test;

197   P=0.26 for Egger's test), and IL-1β (P=0.60 for Begg's test; P=0.14 for Egger's test).

198   **Discussion**

199   The key findings of this study were that that soy intake had no significant effect on IL-6, IL-

200   1β, IL-2 and IFN-γ, but did yield significant reductions in TNF-α. After conducting subgroup

201   analysis, we found that the beneficial effect of soy intake on TNF-α was only evident in parallel

202   designed studies, at dosages ≥100 mg of isoflavones, and in unhealthy subjects. However, the

203   lack of significant benefit of soy in cross-over studies and healthy subjects was likely due to

204   limited power, with only 6 studies for each subgroup. Indeed, the power of a meta-analysis

205   strongly depends on number of included studies (Turner). Chronic inflammation, colloquially

206   termed the "silent killer", acts as a strong disease-promoting factor in a variety of disorders,

207   including arteriosclerosis, obesity, and cancer [58]. Although a review article previously

208   reported the effect of soy and soy product on CRP, there is no systematic review and meta-

209   analysis regarding other inflammatory markers such as TNF-α, IL-6, IL-1β, IL-2 and IFN-γ. A

210   previous meta-analysis reported a non-significant reduction in serum hs-CRP following soy

211   products consumption [29], which is comparable to our results regarding IL-6, IL-1β, IL-2 and

212   IFN-γ. In contrast, however, we found that soy intake had a favorable effect on TNF-α.

213 Therefore, it is possible that the effect of soy intake may not be comparable on all inflammatory

214 markers.

215 In this meta-analysis of clinical trials, we found that soy and soy products consumption had no

216 significant effect on IL-6. However, calculated confidence interval (CI) for the effect of soy

217 nut consumption was very close to the significant increase threshold. Indeed, it may be due to

218 the fact that soy nut is usually consumed in roasted and salted forms. Also, the CI was very

219 close to statistical significance in IL-6 measured in crossover studies. Although crossover

220 studies are more powerful in controlling confounding variables, the number of these studies

221 was low compared with parallel designed studies. Nevertheless, although statistical

222 significance was not formally attained, these results should not be simply overlooked and future

223 studies should further investigate the potential of soy on IL-6.

224 Our findings showed that, in contrast to "healthy" and "overweight or obese" subgroups, soy

225 intake had a significant effect on reducing TNF-α level in unhealthy subjects. Included studies

226 in the "unhealthy" subgroup enrolled overweight, obese, or normal weight participants with

227 prostate cancer, metabolic syndrome, irritable bowel syndrome, hypercholesterolemia,

228 rheumatoid arthritis, climacteric syndrome, Hashimoto's thyroiditis, asthma, non-alcoholic

229 fatty liver disease, or hypertension. Studies in the "overweight and obese" subgroup recruited

230 healthy, overweight, and obese subjects. A previous study showed that the pattern of

231 inflammation is different between healthy and unhealthy obese subjects [59], indicating that soy

232 intake may be effective against high levels of TNF-α, as observed in unhealthy, morbidly obese,

233 patients.

234 We observed that parallel designed studies reported a significant effect of soy intake on TNF-

235 α level. In contrast, however, crossover studies showed no effect. Although cross-over studies

236 are more precise in controlling for confounding variables, the number of these studies was low

237 (n=5) compared with parallel designed studies (n=17); highlighting that more cross-over

238 studies should be undertaken in this regard.

239 According to our findings, only soy isoflavones consumption yielded a reduction in TNF-α.

240 Isoflavones are major phytoestrogens in soy beans and structurally similar to 17-beta-estradiol

241 [60]. Genistein, daidzein, and glycitein were the types of soy isoflavones used in included

242 studies. The bioavailability of isoflavones is more than other flavonoids [61]; indeed, Ganai et

243 al. reported that genistein reduced nitric oxide (NO) and prostaglandin E2 (PGE2), and

244 suppressed production of d-galactosamine-induced proinflammatory cytokines including TNF-

245 α in Wistar rats [62]. Moreover, a previous study, in a murine model, showed that daidzein

246 inhibits TNF-α-induced protein poly-adenosine diphosphate-ribosylation [63]. Tanaka et al.

247 illustrated that daidzein suppresses the Lipopolysaccharide (LPS)-induced TNF-α expression

248 [64], whilst genistein can reportedly prevent insulin receptor substrate-1 (IRS-1) serine

249 phosphorylation through 5'-adenosine-monophosphate-activated protein kinase (AMPK) [65].

250 Indeed, AMPK activation has a substantial role in anti TNF-α property of genistein [65].

251 The beneficial effects of soy isoflavones may be related to equol,, a specific estrogenic

252 metabolite of daidzein produced by bacteria in the gut[66]. Indeed, some evidence suggests that

253 differences in equol production between humans (between racial/ethnic groups) may explain

254 the reported differences in beneficial effects [67]. In the present meta-analysis, the conversion

255 of isoflavones to equol was only measured in two studies[36; 37], therefore, we were unable to

256 include the conversion of isoflavones to equol in our analysis.

257 Although soy protein has some beneficial effects on health; high intake or prolonged

258 consumption of soy protein or raw soybean can be harmful to health. Indeed, soy protein an

259 have adverse effects on the endocrine glands, liver, and kidney, and elicit carcinogenic effects

260 on the breast, pancreas, and thyroid gland [68]. Moreover, soy genistein can induce formation

261 of mutagenesis and carcinogenesis, and proliferation of implanted human breast cancer cells

262 [69]. Therefore, high consumption of soy and soy products should not be advocated.

263 The current meta-analysis has some strengths that should considered. The sample size was

264 large, because we were able to include 28 articles (1816 participants). Both Egger's and Begg's

265 tests indicated no evidence for publication bias. Finally, a comprehensive, pre-defined,

266 subgroup analysis was run. Despite the aforementioned strengths, there are a number of

267 limitations that should be considered: *1*) insufficient follow-up duration in some studies, and

268 *2*) the results of most included studies were not adjusted for confounding factors. However,

269 with regard to these three principle limitations, they were out of the operational control of the

270 study.

271 **Conclusion**

272 In conclusion, the present systematic review and meta-analysis indicated that soy and soy

273 products consumption had no effect on inflammatory biomarkers; IL-6, IL-1β, IL-2, and IFN-

274 γ. A significant reduction was only observed on TNF-α in some specific subgroups. The authors

275 advocate that further, well-controlled, studies should be conducted to clarify the safety and

276 efficacy of soy intake on inflammatory biomarkers.

280 **Conflict of Interest**

281 The authors declare no conflict of interest.

282 **Authors' contributions:**

283   M.R and M.H.R conceived the idea of study and searched databases. M.R and F.M screened

284   the articles. M.R, F.M, and M.H.R extracted data. M.R and F.M drafted the manuscript. M.H.R

285   performed the statistical analysis. C.C and M.H.R revised the manuscript.

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Table 1. Cochrane risk of bias assessment

Domain	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (Performance bias)	Blinding of outcome assessment (Detection bias)	Incomplete outcome data (Attrition bias)	Selective reporting (Reporting bias)	Other sources of bias	Score	Overall quality
Jenkins (2002)	-	-	-	-	-	+	+	2	Fair
Hilpert (2005)	+	-	-	-	+	+	+	4	Good
Borchers (2006)	+	+	+	+	+	+	+	7	Good
Azadbakht (2007)	+	-	-	-	+	+	+	4	Good
Maskarinec (2008)	+	-	-	-	+	+	+	4	Good
Nasca (2008)	-	-	-	-	-	+	+	2	Fair
Beavers(2009)	+	-	-	-	+	+	+	4	Good
Charles (2009)	+	+	+	+	+	+	+	7	Good
Faghih (2009)	+	-	-	-	+	+	+	4	Good
Llaneza (2011)	+	+	-	-	+	+	+	5	Good
Christie(2010)	+	+	+	+	+	+	+	7	Good
Napora (2011)	+	+	+	+	+	+	+	7	Good
Llaneza (2012)	+	-	-	-	-	+	+	3	Good
Ma (2011)	+	+	-	-	+	+	+	5	Good
Sima˜o (2012)	+	-	-	-	+	+	+	4	Good
Kwak (2012)	+	-	+	+	-	+	+	5	Good
Rebholz1 (2012)	+	+	+	+	+	+	+	7	Good
Chi(2013)	+	+	+	+	+	+	+	7	Good
Lebon(2014)	+	+	+	+	+	+	+	7	Good
Smith(2015)	+	+	+	+	+	+	+	7	Good
Mohammad-Shahi (2015)	+	-	-	-	+	+	+	4	Good
Ho (2016)	-	-	+	+	-	+	+	4	Good
Weiland (2016)	+	+	+	+	+	+	+	7	Good
Zhang (2016)	+	+	+	+	+	+	+	7	Good

Nadadur (2016)	+	+	-	-	+	+	+	5	**Good**
Amanat(2017)	+	+	+	+	+	+	+	7	**Good**
Giolo(2018)	+	+	+	+	+	+	+	7	**Good**
Jalili(2019)	+	+	+	+	+	+	+	7	**Good**

†The overall quality of each study was considered as good (>2 '+' signs), fair (2 '+' signs), or weak (<2 '+' sign), respectively.

First author (publication year)	Country	Sample size (Male/Female)	Age (y)	RCT design (Blinding)	Follow-up (Week)	Intervention of experimental group	Intervention of control group	Reported outcomes	Notes about subjects
Jenkins (2002)	Canada	41(23/18)	62	Crossover (Yes)	4 weeks	50 g/d soy protein (73 mg/d isoflavone)	low-fat dairy food	IL-6,TNF-α	hypercholesterolemic men and postmenopausal women
Hilpert (2005)	United States	32(14/18)	58	Crossover(No)	6 weeks	diets containing 25 g/d soy protein (+90 mg/d isoflavones)	25 g/d milk protein	IL-6	Moderately Hypercholesterolemic Adults
Borchers (2006)	United States	37(0/37)	56	Parallel(Yes)	16 weeks	706 mL soymilk/d(71.6 mg isoflavones)+placebo supplement	706 mL cow milk/d +placebo supplement	IFN-γ,TNF-α,IL-2	Healthy postmenopausal women
Azadbakht (2007)	Iran	42(0/42)	NR	Crossover (No)	8 weeks	Soy protein+DASH diet	DASH diet	TNF-α ,IL-6,IL-2	postmenopausal women with the metabolic syndrome
Maskarinec (2008)	United states of America	20(20/0)	59	Crossover(No)	12 weeks	High-soya diet (69 mg isoflavone per day)	low-soya diet(less than 5 mg isoflavone per day)	IL-6	Healthy men
Nasca (2008)	United States	60(0/60)	56	Crossover (No)	8 weeks	TLC diet + soy nuts (101 mg isoflavones)	TLC diet	IL-6	Healthy postmenopausal normotensive or hypertensive women
Beavers(2009)	United States	31(0/31)	54	Parallel (Yes)	4 weeks	consume 3 servings of vanilla soy milk	reduced fat dairy milk	TNF-α ,IL-6, IL-1β	Healthy,recreationally active ,postmenopausal women
Charles (2009)	United States	75(0/75)	57	Parallel(Yes)	12 weeks	20 g soy protein (160 mg of total Isoflavones)	20 g of whole milk protein	TNF-α ,IL-6	Healthy postmenopausal women
Faghih (2009)	Iran	41(0/41)	38	Parallel(No)	8 weeks	soy milk diet (three servings of calcium fortified soy milk)	high milk diet (three servings of low fat milk)	TNF-α,IL-6	Premenopausal overweight and obese women
Llaneza (2011)	Spain	70(0/70)	57	Parallel(No)	24 weeks	1200 kcal diet+ exercise+ 200mg Glycine max(corresponded to 80mg of isoflavone)	1200 kcal diet+ exercise	TNF-α	Healthy obese postmenopausal women
Christie(2010)	Italy	33(0/33)	52	Parallel (Yes)	12 weeks	Shake + 20 g soy protein (160 mg isoflavones)	Shake	IL-6,TNF-α	Postmenopausal caucasian and african american women
Napora (2011)	United states	33(33/0)	69	Parallel (Yes)	12 weeks	20 g soy protein (160 mg Isoflavones)	20 g whole milk protein	IL-6,TNF-α	Androgen deprived men with prostate cancer
Llaneza (2012)	Spain	65(0/65)	57	Parallel(No)	96 weeks	physical exercise+ Mediterranean diet +200mg Glycine max(corresponded to 80mg of isoflavone)	physical exercise+ Mediterranean diet	TNF-α	Postmenopausal women
Ma (2011)	China	90(26/64)	51	Parallel(Yes)	8 weeks	soy isolate protein(18 g soy protein, 6 g milk protein)	24 g of milk protein	TNF-α	Moderately hypercholesterolemic chinese adults
Sima˜o (2012)	Brazil	30(0/30)	48	Parallel(No)	12 weeks	29 g/d soyabean (kinako)	Usual diet	TNF-α,IL-6	Women with the metabolic syndrome
Kwak (2012)	Korea	64(27/37)	37	Parallel(Yes)	12 weeks	4.5 g/d black soy peptide	3.9 g/d casein	TNF-α,IL-1β	Overweight and obese
Rebholz1 (2012)	United States of America	51(NR)	46	Crossover (Yes)	8 weeks	40 g soybean protein (89.3 mg isoflavones)	40 g of milk protein supplement	IL-6,TNF-α	Adults in New Orleans, Louisiana and Jackson, Mississippi
Chi(2013)	China	70(0/70)	50	Parallel(Yes)	24 weeks	90 mg/day isoflavone+5 mcg Vitamin D	Starch+ Vitamin D	TNF-α ,IL-6	Chinese women suffering from climacteric syndrome
Lebon(2014)	Canada	34(0/34)	59	Parallel(Yes)	24 weeks	70 mg isoflavones +exercise	cellulose+exercise	IL-6, TNF-α	Overweight and obese postmenopausal women
Smith(2015)	United States	386(132/254)	36	Parallel (Yes)	24 weeks	98 mg isoflavone	matching placebo(less than 0.05mg isoflavone)	IL-6	Poorly controlled asthma

Mohammad-Shahi (2015)	Iran	25(0/25)	46	Crossover(No)	4 weeks	diet containing soy milk	diet containing cow's milk	TNF-α,IL-1β,IL-6	Women with rheumatoid arthritis
Ho (2016)	Singapore	18(6/12)	35	Crossover (Yes)	4 weeks	20 g Soy milk powder (2.0g free plant sterols)	20 g Soy milk powder placebo	TNF-α	Healthy adults
Weiland (2016)	Germany	57(57/0)	63	Parallel(Yes)	7 weeks	milk enriched with 2·8 g soya - phospholipids	milk enriched with 3 g milk-phospholipids	IL-6	Overweight or obese men
Zhang (2016)	China	218 (0/218)	42	Parallel(Yes	4 weeks	600 mg/d genistein	placebo	TNF-α, IFN-γ, IL-2,IL-6 ,IL-10	Hashimoto's thyroiditis patients
Nadadur (2016)	United States	37 (0/37)	58	Parallel (Yes)	8 weeks	15 g soy protein (50 mg isoflavones)	Control diet	IL-6,TNF-α	Healthy postmenopausal women
Amanat(2017)	Iran	78(NR)	43	Parallel (Yes)	8 weeks	250 mg genistein	Cornstarch	IL-6,TNF-α	Non-alcoholic fatty liver disease
Giolo(2018)	Brazil	32(0/32)	60	Parallel(Yes)	10 weeks	100 mg isoflavones+ exercise training	100 mg of cornstarch+ exercise training	IL-6	Non-obese, postmenopausal women
Jalili(2019)	Iran	46(0/46)	41	Parallel(Yes)	6 weeks	40 mg/d soy isoflavones	Corn starch	TNF-α	Female patients with irritable bowel syndrome

Table 2. Characteristics of included clinical trials in meta-analysis.

IL: Interleukin; TNF-α: Tumor necrosis factor α; IFN-γ: Interferon γ; TLC diet: Therapeutic lifestyle change; NR: Not reported

	Subgroup		Studies (n)	Effect size	I^2	P heterogeneity	P between subgroup heterogeneity
IL-6 (pg/ml)	Gender	male	4	0.14(-0.18,0.45)	15.1%	0.316	<0.001
		female	15	0.15(-0.08,0.39)	69.9%	0.000	
		both	2	0.02(-0.64,0.67)	0.0%	0.989	
		NR	2	-0.57(-1.50,0.36)	89.6%	0.002	
	Age(year)	<60	17	0.04(-0.24,0.32)	77.6%	0.000	0.813
		≥60	5	0.17(-0.20,0.53)	42.5%	0.138	
	RCT design	Parallel	14	-0.05(-0.39,0.29)	80.5%	0.000	0.666
		Crossover	9	0.18(-0.02,0.38)	31.8%	0.163	
	Follow-up (week)	<12	15	0.07(-0.20,0.34)	78.8%	0.000	0.454
		≥12	8	0.06(-0.24,0.36)	40.3%	0.110	
	Soy-type	soy protein	9	0.02(-0.19,0.22)	39.4%	0.105	0.150
		isoflavone	6	0.03(-0.71,0.77)	90.6%	0.000	
		soy milk	4	-0.02(-0.39,0.34)	25.8%	0.257	
		soy nut	4	0.27(-0.02,0.55)	0.0%	0.437	
	Dose(mg)	<100	8	0.19(-0.09,0.47)	46.6%	0.070	0.808
		≥100	8	-0.07(-0.58,0.44)	88.3%	0.000	
		NR	7	0.07(-0.11,0.25)	0.0%	0.513	
	Subject	healthy	5	0.04(-0.26,0.34)	41.9%	0.142	0.079
		unhealthy	12	0.15(-0.21,0.51)	81.9%	0.000	
		NR	3	-0.22(-0.60,0.15)	29.2%	0.243	

TNF-α (pg/ml)	Subgroup	Level	N	Effect (95% CI)	I²	p	p-subgroup
		overweight or obese	3	0.14(-0.19,0.48)	0.0%	0.563	
	Gender	male	2	-0.07(-0.50,0.37)	0.0%	0.483	
		female	16	-0.32(-0.63,-0.02)	85.7%	0.000	0.961
		both	3	-0.11 (-0.44,0.22)	25.1%	0.263	
		NR	2	-0.51(-1.51,0.50)	94.0%	0.000	
	Age(year)	<60	19	-0.36(-0.62,-0.09)	84.8%	0.000	
		≥60	3	0.04(-0.32,0.40)	0.0%	0.535	0.065
	RCT design	Parallel	17	-0.35(-0.66,-0.03)	84.6%	0.000	
		Crossover	6	-0.06(-0.24,0.13)	50.0%	0.075	0.001
	Follow-up (week)	<12	13	-0.40(-0.67,-0.14)	85.7%	0.000	
		≥12	10	-0.09(-0.47,0.29)	78.2%	0.000	0.879
	Soy-type	soy protein	10	-0.04(-0.12,0.05)	0.0%	0.487	
		isoflavone	5	-1.00(-1.94,-0.06)	94.4%	0.000	0.000
		soy milk	5	-0.39(-0.90,0.11)	63.7%	0.026	
		soy nut	3	0.18(-0.16,0.52)	20.0%	0.287	
	Dose(mg)	<100	10	-0.30(-0.73,0.13)	89.4%	0.000	
		≥100	5	-0.47(-0.79,-0.14)	58.1%	0.049	0.007
		NR	8	-0.15 (-0.45,0.15)	66.4%	0.004	
	Subject	healthy	5	-0.28(-0.56,0.01)	27.3%	0.240	
		unhealthy	11	-0.56(-0.97,-0.14)	90.3%	0.000	
		NR	3	-0.04(-0.17,0.09)	0.0%	0.494	0.005
		overweight or obese	4	0.25(-0.02,0.52)	0.0%	0.552	

Table 3. Result of subgroup analysis of included studies in meta-analysis