Effects of soy protein containing isoflavones on women's lipid profile: a meta-analysis

Efeitos do consumo de proteína de soja contendo isoflavonas sobre a concentração de lipídeos séricos em mulheres: metanálise

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ABSTRACT

This study evaluated the effects of soy protein containing isoflavones on the lipid profile of women. A meta-analysis including 13 eligible randomized controlled trials was carried out. The literature was systematically searched for randomized controlled trials on the effects of soy protein containing isoflavones on the serum lipids of adult women. The main searched databases were PubMed, Cochrane Library, MedLine, Lilacs and Web of Science. Randomized controlled trials were included if they met the following criteria: published from 1966 to 2005, the study population consisted of women only, had either a crossover or a parallel design and the amounts of soy protein and isoflavones consumed were provided. Weighted mean effect sizes were calculated for net changes in serum lipid concentrations using fixed-effects and random-effects models. Prespecified subgroup analyses were performed to explore the influence of covariates on net lipid change. Soy protein with isoflavones was associated with a significant decrease in total serum cholesterol (by 5.34mg/dL, or 2.4%, p=0.03). No significant associations were detected for low density lipoprotein-cholesterol, triacylglycerols and high density lipoprotein-cholesterol. Amounts of soy protein greater than 40g decreased total cholesterol by 6.56mg/dL (95% CI: -12.35 to -0.39, p=0.04). Soy protein supplementation had small statistically significant effects on the total serum cholesterol of women, but they were clinically insignificant. Furthermore, there were no statistically significant effects on serum low density lipoprotein-cholesterol, high density lipoprotein-cholesterol or triglycerides.


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RESUMO

Avaliar o efeito da proteína de soja isolada contendo isoflavonas sobre os níveis de lipídeos séricos em mulheres adultas através de uma metanálise. Realizou-se uma busca sistemática de artigos nos bancos de dados Cochrane Library, MedLine e Web of Science databases. Foram selecionados somente ensaios clínicos randomizados que apresentavam os seguintes critérios: desenho do estudo paralelo ou crossover, publicados entre 1966 e 2005, sujeitos do sexo feminino, especificação da quantidade administrada de proteína de soja isolada contendo isoflavonas. Após criteriosa seleção e análise da qualidade dos estudos, conduziu-se uma metanálise incluindo 13 ensaios clínicos randomizados. O efeito do consumo de proteína de soja isolada sobre os níveis de lipídeos séricos foi calculado utilizando-se os modelos de efeito fixo e efeitos aleatórios. Realizou-se análise em subgrupos para avaliar a influência de covariables sobre alterações dos níveis de lipídeos sanguíneos. A metanálise mostrou que o consumo de proteína de soja isolada está associado à diminuição do colesterol-total (-5,34mg/dL, ou 2,4%, p=0,03). Não se encontraram alterações significativas ao avaliar o lipoproteína de baixa densidade-colesterol, os triglicerídeos e o lipoproteína de alta densidade-colesterol. O consumo de proteína de soja isolada, em quantidades maiores ou iguais a 40g/dia, reduziu os níveis de colesterol-total em 6,56mg/dL (95% IC: -12,35 a 0,39, p=0,04). Os achados sugerem efeitos estatisticamente significativos de pequena magnitude sobre os níveis de lipídeos séricos em mulheres, mas clinicamente insignificativos. Além disso, não foram encontrados efeitos estatisticamente significativos sobre a concentração sérica de lipoproteína de baixa densidade-colesterol, lipoproteína de alta densidade-colesterol ou triglicerídios.


INTRODUCTION

The beneficial effects of soy protein on serum lipids have been extensively studied in the last decades1-4. The classic Anderson et al.1 meta-analysis showed that an average daily intake of 47g of soy protein was associated with a 9.3% reduction in total serum cholesterol, 12.9% reduction in Low Density Lipoprotein-cholesterol (LDL-c), and 10.5% reduction in triacylglycerols. According to the IV Diretriz Brasileira sobre Dislipidemia e Prevenção de Aterosclerose, a daily intake of 25 grams of soy reduces plasma cholesterol (LDL-c) by 6%5.

However, the optimal soy and isoflavones intake has also been debated. Anderson et al.1 reported that an intake of 47g/d of soy protein has a beneficial effect, but the authors did not specify how much isoflavones were consumed. Zhuo et al.3 suggested an average intake of 50g/d of soy protein with high isoflavone concentration (86mg/d). Weggemans & Trautwein4 did not find a dose-response relationship between soy-associated isoflavones and changes in LDL or High Density Lipoprotein-cholesterol (HDL-c). Zhan & Ho4 suggested that a daily intake of 80mg or more of isoflavones has a better effect on the lipid profile. In 1999, the US Food and Drug Administration (FDA) recommended an intake of at least 25g of soy protein daily as part of a low fat diet, which in turn, may reduce the risk of heart disease6. In 2007, the FDA announced its intent to reevaluate the scientific evidence for soy protein intake and the risk of coronary heart disease using its newly proposed evidence-based guideline7.

Many questions remain unanswered. There is a lack of consistency on whether the changes in lipid profile are due mainly to isoflavones and what amount of soy protein containing isoflavones is most beneficial. Another problem is that most trials pool together men and women in their analyses. A recent meta-analysis4 showed that total cholesterol and LDL-c were greater reduced in men than in women, suggesting that the effect of soy protein may vary according to gender. In addition, a review on soy protein, isoflavones and cardiovascular health showed that, although soy protein, as compared with others proteins, mainly milk protein, may have an effect on LDL-c, its effect on other CVD risk factors has not been confirmed by studies done in the last 10 years8. Furthermore, the quality of the studies included in the previous meta-analysis has not been assessed.
The main objective of this meta-analysis was to investigate the effect of soy protein containing isoflavones (ISP) on the serum concentrations of total cholesterol, LDL-c, triacylglycerol and HDL-c in adult women.

**METHODS**

**Identification and selection studies**

The medical literature was systematically searched for randomized controlled trials published from 1966 to March 2005 on the effects of soy protein containing isoflavones on the serum lipids of women. The main searched databases were PubMed, Cochrane Library, Lilacs and Web of Science. The searched keywords were: “soy”, “soy protein”, “soybean proteins” “women”, “female”, “cholesterol”, and “randomized controlled trial”. The Grey Literature was also searched: System for Information on Grey Literature (SIGLE), National Technical Information Service (NTIS), Trials Central and Current Controlled Trials, but no relevant studies were found. The references of the selected studies were also examined. Language was not a selection criterion but only trials published in English met the inclusion criteria.

Randomized controlled trials were included if they met the following criteria: published from 1966 to March 2005, the study population consisted only of adult women, the design was either crossover or parallel and the amounts of soy protein and isoflavones consumed were provided.

Studies were excluded if there was no control group; if the amounts of soy protein and isoflavones, and the lipid concentrations, both at baseline and following the intervention were not provided; if other substances that could affect serum lipid levels were also given to participants; and if they included subjects with a history of chronic diseases that could affect lipid concentrations. A total of 15 studies were eligible according to the above criteria.

Three independent reviewers assessed the quality of the studies before inclusion in the meta-analysis. The following items were considered: took into account the generation of randomization sequence, allocation concealment, blinding, compliance with the intervention, and analysis by intention to treat. Each trial was given a score from 0 to 10. Two articles were excluded during this phase because their scores were very low; thus, 13 articles were selected for the meta-analysis.

**Data extraction and analysis**

The meta-analysis was conducted using Revman 4.2.7 and Stata 7 software. The outcome variables considered for the analysis were total cholesterol, LDL-c, HDL-c and triacylglycerol recorded as continuous variables.

The estimate of effect was defined as the mean difference (net change in mg/dL) between the change in lipid concentrations in subjects consuming soy protein with isoflavones (final value minus initial value) and in subjects consuming the control diet.

In studies with more than one treatment group (soy protein) the effect of all groups were compared with the control group, except those groups with very low soy concentration (ISP ≤ 4.4mg), which were excluded from the analysis (Table 1). This was because such low concentrations were similar to those given to subjects in some control groups.

For the computation of pooled effects, we used the weighted mean difference and each study was assigned a weight consisting of the reciprocal of its variance. Fixed-effects models were used for the main results because no heterogeneity (p≥0.05) or inconsistencies (I²=0) among the studies were detected. Random-effects models were used in subgroup analyses that showed some level of heterogeneity or inconsistency.

To explore the possible influence of covariates on the net change in lipid concentrations,
subgroup analyses were also done according to initial lipid concentrations, menopausal status, study design (parallel or crossover), concentration of isoflavones (≤40mg; 41.1 to 79.9mg; ≥80mg), length of follow-up (6 to 8wk; 12wk; 24 to 60wk), and type of diet (usual or low fat diet).

Finally, to examine potential publication bias, Standard Errors (SE) of the study effects were plotted against their corresponding effect sizes and Begg’s and Egger’s tests were performed.

**RESULTS**

**Characteristics of the studies**

Table I shows selected characteristics of the 13 studies that met the eligibility criteria, yielding 18 comparisons. Overall, 772 women were included in the meta-analysis. The size of the studies varied from 13 to 175 subjects per study. The mean age of the women was 54.6 years (18 to 75 year-olds). Most studies included postmenopausal women. In six studies, women were hypercholesterolemic at baseline. Seven studies used a parallel randomized design, and six used a crossover design. All studies used isolated soy protein containing isoflavones and the median soy protein intake was 40g/day (20 to 63g/day). The median isoflavone concentration was 80mg (2 to 132mg/day). Trials varied in length from 6 to 60 weeks, with a median duration of 12 weeks. Control groups received casein, milk protein, and whey protein, complex carbohydrates, and ISP with traces of or no isoflavone content. In two studies all participants were instructed to follow a National Cholesterol Education Program (NCEP) step I diet during the study (<30% dietary energy as total fat, <10% energy as saturated fat and <300mg/day of cholesterol).

<table>
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<tr>
<th>Author</th>
<th>N</th>
<th>Soy protein (g)</th>
<th>Isof (mg)</th>
<th>Intervention/Control</th>
<th>Duration (wk)</th>
<th>Initial lipid (mg/dL)</th>
<th>Menopausal</th>
<th>Initial TC (mg/dL)</th>
<th>Design RC²</th>
<th>Type of diet</th>
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<td>66</td>
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<td>90</td>
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<td>Pre</td>
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¹Isoflavones; ²Randomized Controlled trial; ³excluded from the analysis; ⁴Isolated Soy Protein; ⁵Isolated soy protein with traces of isoflavone; ⁶Isolated Soy Protein without isoflavones; ⁷Complex carbohydrates; ⁸Hypercholesteremia; ⁹Normo and hypercholesterolemia; ¹⁰Normocholesteroloma; ¹¹Postmenopausal; ¹²Premenopausal; ¹³Premenopausal; ¹⁴NCEP SI - National Cholesterol Education Program (NCEP) step I diet (<30% dietary energy from total fat, <10% energy from saturated fat and <300mg/day of cholesterol).
Quality assessment

All papers reported a randomized design, but only 2 studies described the random sequence generation and the adopted allocation concealment. With regard to blinding, all studies reported double-blinding, but only 6 provided a further description of the blinding procedures or the nature of the placebo. In most of the articles, losses to follow-up were stated or deducible from tables. Only 1 study used intention-to-treat analysis. The mean quality score was 6.3.

Changes in serum lipid concentrations

A statistically significant effect of soy protein containing isoflavones was observed only in the outcome total cholesterol (Figure 1). Total cholesterol decreased in the soy protein group compared with the corresponding control group in 13 (72%) of the 18 comparisons. The pooled estimate of the effects of the intervention on total cholesterol was a decrease of 5.34mg/dL (95% CI: -10.30 to -0.38; p=0.03), or 2.4%.

Soy protein intake did not affect serum LDL-c, HDL-c and triacylglycerol levels significantly. LDL-c decreased in the group consuming soy protein containing isoflavones compared with the corresponding control group in 13 (81%) of the 16 comparisons in which LDL-c was measured (Figure 2). Only 3 comparisons (18%) reported an increase of this outcome. The pooled estimate of the effects of consuming soy protein containing isoflavones on LDL-c was a decrease of 3.50mg/dL (95% CI: -8.31 to 1.32; p=0.16), or 2.4%. There was a net change decrease in serum triacylglycerol concentration of 8.86mg/dL (95% CI: -19.12 to 1.40; p=0.09), or 5.9% (data not shown).

![Figure 1](image-url)

**Figure 1.** Net change (and 95% CI) in total cholesterol (mg/dL) associated with intake of soy protein containing isoflavones.

Note: WMD: weighted mean difference; fixed: fixed-effect model. Heterogeneity chi-squared=11.36 (d.f.=17) p=0.837; Estimate of between-study variance Tau-squared=0.0000; Test of WMD=0 : z=2.11 p=0.035.
showed in figures). Fourteen studies (82%) reported a net reduction and three studies (18%) reported an increase. HDL-c increased in the group consuming soy containing isoflavones compared with the corresponding control group in 12 (71%) of the 17 comparisons in which it was measured. The overall pooled estimate of the effect of soy protein containing isoflavones was 0.91mg/dL for HDL-c (95% CI: -1.38 to 3.19; \( p = 0.44 \)), or 1.08% (Figure 3).

**Subgroup analysis**

In the subgroup analyses, the pooled estimates of soy protein effect on total cholesterol was significant when soy protein intake exceeded 40g (\( p = 0.04 \)), in crossover-design studies (\( p = 0.05 \)), and in those in which the subjects were on their usual diets (\( p = 0.05 \)); the significance was borderline in studies with the shortest intervention time (6 to 8wk) (\( p = 0.07 \)), and those including both normal and hypercholesterolemic subjects (\( p = 0.08 \)) (Table 2). With regard to other outcomes, there were no significant results except for borderline significance regarding LDL-c in the subgroup consuming ≥40g of soy protein (mean change=-5.02mg/dL; 95% CI: -11.20 to 0.77; \( p = 0.09 \)). Although not statistically significant, a gradient was observed in relation to the isoflavone concentration used in the treatment groups. The effect was stronger in groups consuming higher concentrations (≥80mg de isoflavones).

![Figure 2](image-url)  
*Figure 2. Net change (and 95% CI) in LDL-cholesterol (mg/dL) associated with intake of soy protein containing isoflavones.

Note: WMD: weighted mean difference; fixed: fixed-effect model. Heterogeneity chi-squared=3.95 (d.f.=15) \( p = 0.998 \); Estimate of between-study variance Tau-squared = 0.0000; Test of WMD=0: \( z = 1.42 \) \( p = 0.155 \).*
**Discussion**

The present meta-analysis investigated the effect of soy protein containing isoflavones on the serum lipid levels of women. The results showed that there was a significant decrease (-5.34 mg/dL) in total serum cholesterol following diet supplementation with soy protein. Similar, but greater effects were reported by Anderson et al.\(^1\) (-23.17 mg/dL) and Zhan & Ho\(^4\) (-8.49 mg/dL). One possible explanation for this difference is that most of the studies included in the Anderson et al.\(^1\) meta-analysis contained subjects with much higher baseline serum cholesterol levels and their interventions contained larger amounts of soy protein. In addition, these meta-analyses pooled together men and women in their analyses. Our study population included only women, and several studies included normocholesterolemic women. In fact, the effect size of our study was similar to those reported by Zhan & Ho\(^4\) for women, in a sub-group analysis according to gender. The authors also reported greater reductions of total cholesterol in men, suggesting that gender may have a modifying effect, with possibly smaller effects among women (-6.18 mg/dL). No significant associations were reported elsewhere\(^2,3\).

No statistically significant effects were found for LDL-c, HDL-c and triacylglycerol by the present study. However, this may be due to
type-II error. It may be due to the relatively small number of studies, and therefore total size, resulting in a reduced power of detecting significant effects of the intervention. To some extent, the effect size found in the present study is similar to that reported by Zhan & Ho 4. The net change in our result was -3.50mg/dL for LDL-c, -8.86mg/dL for triacylglycerol and 0.91mg/dL for HDL-c; whereas Zhan and Ho4 reported -5.40mg/dL, -5.31 mg/dL and 0.77mg/dL, respectively. That is, the present meta-analysis was consistent with previously reported results for women.

The soy components responsible for the beneficial effects on the cholesterol levels and their mechanisms of action on the lipid profile are still being investigated. Most studies support the ‘isoflavone hypothesis’23,24. Isoflavones are structurally similar to estrogen and bind to its receptors, promoting a weaker estrogenic response, with beneficial effects on lipid metabolism25. The literature seems to confirm this beneficial effect1,4. Although the results were not significant, the present study found that apparently there is a biological gradient in studies with higher concentrations of isoflavones (≥80mg) in the treatment groups that experienced greater cholesterol reduction (-8.88 mg/dL; IC 95%: -23.55 to 5.4) (Table 2). Several studies have reported a greater reduction in blood lipids when soy protein was combined with isoflavones (compared with absence of isoflavones)10,15,19,21,26. However, some studies assessed the lipid-lowering effect of isolated isoflavones (without its protein component) on postmenopausal women and found no differences27,28.

### Table 2. Pooled estimates of the treatment effect on total cholesterol in subgroups of trials defined by participant and study design features.

<table>
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<tr>
<th>Variables</th>
<th>N° of trials</th>
<th>Sample size</th>
<th>Net change (95%CI) (mg/dL)</th>
<th>p</th>
<th>Test of heterogeneity p</th>
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<td></td>
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<td>Crossover</td>
<td>9</td>
<td>459</td>
<td>-6.56 (-13.13, 0.00)</td>
<td>0.05</td>
<td>1.00</td>
</tr>
<tr>
<td>Parallel</td>
<td>9</td>
<td>588</td>
<td>-4.25 (-13.13, 4.25)</td>
<td>0.36</td>
<td>0.29b</td>
</tr>
<tr>
<td>Diet</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Usual</td>
<td>15</td>
<td>923</td>
<td>-5.40 (-10.42, 0.00)</td>
<td>0.05</td>
<td>0.66</td>
</tr>
<tr>
<td>Low-fat</td>
<td>3</td>
<td>124</td>
<td>-6.18 (-21.62, 9.65)</td>
<td>0.44</td>
<td>0.97</td>
</tr>
<tr>
<td>Soy protein amount (g)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;40</td>
<td>4</td>
<td>373</td>
<td>-3.09 (-11.97, 5.79)</td>
<td>0.51</td>
<td>0.56</td>
</tr>
<tr>
<td>≥40</td>
<td>14</td>
<td>674</td>
<td>-6.56 (-12.35, -0.39)</td>
<td>0.04</td>
<td>0.78</td>
</tr>
<tr>
<td>Isoflavone concentration (mg/d)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤40</td>
<td>4</td>
<td>258</td>
<td>-4.25 (-13.51, 4.63)</td>
<td>0.33</td>
<td>0.54</td>
</tr>
<tr>
<td>41.1 - 79.9</td>
<td>5</td>
<td>216</td>
<td>-6.95 (-17.37, 3.47)</td>
<td>0.19</td>
<td>0.13</td>
</tr>
<tr>
<td>≥80</td>
<td>12</td>
<td>729</td>
<td>-8.88 (-23.55, 5.40)</td>
<td>0.16</td>
<td>0.98a</td>
</tr>
<tr>
<td>Duration (wk)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6-8</td>
<td>5</td>
<td>336</td>
<td>-7.72 (-16.60, 0.77)</td>
<td>0.07</td>
<td>0.91</td>
</tr>
<tr>
<td>12</td>
<td>7</td>
<td>339</td>
<td>-2.32 (-8.88, 4.25)</td>
<td>0.52</td>
<td>0.96</td>
</tr>
<tr>
<td>24-60</td>
<td>6</td>
<td>372</td>
<td>-5.31 (-10.62, -0.39)</td>
<td>0.11</td>
<td></td>
</tr>
</tbody>
</table>

* all studies with <25.6g of soy; **I² = 29.4%; ***I² = 17.7%; ***I² = 44.5%; a, b, c - random effects model.
It is important to remember that soy intake may be affected by an individual’s ability to produce equol (a component produced by humans after soy intake). Equol is an isoflavone metabolite that presents greater affinity for the estrogen receptor than its precursor daidzein. Therefore, metabolic variability needs to be considered: individuals who produce less equol benefit less.

In spite of the apparent dose-response relationship, consistency and biological plausibility, which strengthen the hypothesis of a causal relationship between isoflavones and reduction of total cholesterol, the presence of other soy components cannot be ignored, and they have not been analyzed in most studies. The significant association between the total amount of soy protein consumed and total cholesterol reduction (p=0.04) may also be related to other soy protein components.

Most of the beneficial effects are attributed to isoflavones, natural selective estrogen receptor modulators, whose effects on lipoproteins are similar to those of estrogen, namely decreasing LDL-c and increasing HDL-c.

Nevertheless, soy protein contains other components, such as storage peptides, saponins and fiber. These components have been linked with a decrease in serum lipids, yet they have not been quantified or taken into account by most studies. For example, specific peptides and saponins can affect blood cholesterol levels. Specific peptides from soy proteins can modulate cholesterol homeostasis, eliciting a cholesterol-lowering effect. In addition, saponins may play a role in mediating the hypercholesterolemic activity of soy protein. One of the possible mechanisms by which saponins and fiber can affect cholesterol metabolism is by forming mixed micelles that can interfere in the enterohepatic circulation of bile acids, blocking the reabsorption of bile acids from the terminal ileum.

Discrepancy among findings may be due to the presence or absence of specific components associated with soy protein preparations or unaccounted shifts in the fatty acid, cholesterol, or fiber content of diets used in earlier studies.

Many studies have demonstrated that the reduction in lipid and lipoprotein levels in many people is small, but soy protein consumption produces significant changes overall. These differences are relatively small when taken quantitatively, but they are reported in most studies. They are probably due to many possibilities that go from the chemical quality of the soy protein to the differences of its effect secondary to metabolic complexity and human genetics.

Subgroup analyses showed borderline effects of shorter intervention periods (6 to 8 weeks) on the outcome total cholesterol. A similar result was found by Allen et al. They found that total cholesterol reduced significantly after consuming soy protein with isoflavones for 6 weeks but no further statistically significant reduction was found after 12 weeks. This could also result from diet fatigue, that is, lower product adherence in longer interventions.

Longer interventions were not effective, which raises the possibility of reduced compliance. Only 6 studies analyzed compliance to the intervention by determining urine or serum isoflavone levels. In other studies, compliance relied on participant’s reports or on the number of packages returned but both methods are considered inappropriate.

Fixed-effects models were used for the main results because no heterogeneity or inconsistencies were detected. But in some of the sub-group analyses, the assumption of heterogeneity implied the use of random-effects models. Heterogeneity in these cases can probably be attributed to differences in soy protein and isoflavone intake, study duration and baseline lipid levels across studies.

The present study found some evidence for publication bias when evaluating the outcomes total cholesterol and HDL-cholesterol. However, publication bias is not the only explanation for asymmetrical funnel plots or
significant test results. Other possibilities include true heterogeneity, variation in the methodological quality of the studies, analysis of small studies, confounding heterogeneity due to poor choice of effect measure, and chance. Furthermore, since the present meta-analysis included few studies, care should be exercised when interpreting non-significant results for publication bias tests. Publication bias may exist even with non-significant results. The present study also used more stringent selection criteria leading to improved meta-analysis quality. In addition, each selected study in this meta-analysis had its quality evaluated, something not reported in other meta-analyses. Interpretation of the findings of a study depends on design, conduct and analyses (internal validity), as well as on populations, interventions and outcome measures (external validity). In the present meta-analysis, only a couple of studies detailed the randomization process. Absence of randomization can distort effects in either direction and it is impossible to predict whether bias has been avoided in any particular non-randomized study. Moreover, blinding makes it difficult to bias results intentionally or unintentionally, and so helps to ensure conclusion credibility. Less than 50% of the studies eligible for the present meta-analysis provided further description of the blinding procedures or on the nature of the placebo and the average score was relatively low.

Although the present meta-analysis found a statistically significant reduction in total serum cholesterol due to consumption of soy protein containing isoflavones, this reduction was clinically insignificant. A meta-analysis of 38 large clinical trials including primary and secondary preventions found total cholesterol needs to be reduced by 10% for the risk of mortality from cardiovascular disease to reduce by 15% and the risk of total mortality to reduce by 11%. The present meta-analysis showed that total cholesterol decreased by only 2.4%.

**CONCLUSION**

In summary, these findings suggest small statistically significant effects on the total serum cholesterol of women, but they are clinically insignificant. Furthermore, there were no statistically significant effects on serum LDL-c, HDL-c or triglycerides.

**CONTRIBUTORS**

C.C.C. PREDIGER conceived and designed the study and analyzed and interpreted the data. M.T.A. OLINTO and M.P. PATTUSSI contributed to the conception of the study and data interpretation and data analysis and interpretation, respectively. L.C. NÁCUL and D.R. ZIEGLER contributed to the discussion.

**REFERENCES**


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