Effects of extracted soy isoflavones alone on blood total and LDL cholesterol: meta-analysis of randomized controlled trials

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CRD summary
This review concluded that ingestion of about 70mg/day of extracted soy isoflavones alone for between one and three months did not improve total and LDL cholesterol levels in menopausal women with normal cholesterol; further studies were required to verify the effects of extracted soy isoflavones. This was a generally well-conducted review and the conclusions are likely to be reliable.

Authors' objectives
To evaluate the effects of extracted soy isoflavones alone on total and low density lipoprotein (LDL) cholesterol.

Searching
MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL), Japana Centra Revuo Medicina and China National Knowledge Infrastructure (CNKI) were searched from 1966 to 2007. Search terms were not reported. References of relevant systematic reviews and meta-analyses were searched. Only studies published in English, Japanese or Chinese were eligible for inclusion.

Study selection
Randomised controlled trials (RCTs) with placebo controls that assessed ingestion of extracted soy isoflavones for one to three months in adults were eligible for inclusion in the review. The primary outcomes were levels of low-density lipoprotein (LDL) cholesterol and total cholesterol.

All included studies enrolled menopausal or perimenopausal women. Most studies were designed to maintain the usual diet and lifestyle of participants. Mean baseline values for total cholesterol ranged from 5.40mmol/L to 6.03mmol/L. Most studies were in healthy participants; two assessed women with diabetes and one women with a history of breast cancer. Doses of soy isoflavones ranged from 42mg to 150mg per day. Adverse effects were reported in addition to the primary outcomes.

Two reviewers independently assess the studies for inclusion; disagreements were resolved through discussion.

Assessment of study quality
The studies were assessed with the Jadad scale, which awards up to 5 points based on the criteria of randomisation, blinding and treatment of withdrawals, and dropouts. A score of more than 2 was considered to indicate a high-quality study. It appeared that two reviewers performed the validity assessment.

Data extraction
Two reviewers independently extracted the data, including the final means and standard deviations of total cholesterol and LDL cholesterol in each group. Both plasma and serum concentrations were extracted as reported; no correction for the 3% difference between these values was made. Data extracted were double-checked.

Methods of synthesis
The studies were combined in fixed-effect meta-analyses unless there was statistical heterogeneity that could not readily be explained, when a random-effects model was used. Statistical heterogeneity was assessed using the $X^2$ test and the $I^2$ statistic. Subgroup analyses were carried out based on the variability in baseline total cholesterol and LDL cholesterol, duration of intervention, dose of isoflavones, study design and study quality. A sensitivity analysis that excluded two studies with extremely small standard deviations and differences in baseline values between groups was conducted. Publication bias was assessed using funnel plots.

Results of the review

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Twelve RCTs (n=565) were included in the review. Sample sizes ranged from 22 to 117. Six were cross-over trials and six parallel group trials. Jadad scores ranged from 2 to 5 points.

**Total cholesterol**: An analysis of all 12 RCTs found highly significant statistical heterogeneity (p<0.00001). Therefore, the results of a sensitivity analysis that excluded two studies with extremely small standard deviations and differences in baseline values between groups was presented. This showed a nonsignificant effect of an average intake of soy isoflavones of 73mg/day (0.01 mmol/L, 95% CI -0.12 to 0.14; 10 RCTs). There was no evidence of statistically significant heterogeneity in this analysis.

**LDL cholesterol**: An analysis of the the 10 RCTs that reported LDL cholesterol found highly significant statistical heterogeneity (p<0.003). Therefore, the results of a sensitivity analysis that excluded one trial with significant differences in baseline values between groups were presented. This showed a nonsignificant effect of an average intake of soy isoflavones of 67mg/day (0.03 mmol/L, 95% CI -0.11 to 0.16; nine RCTs). There was no evidence of statistically significant heterogeneity.

The results of subgroup analyses based on whether trials were parallel or cross-over designs, and on whether they lasted for more or less than two months, were also reported. The only significant finding from these analyses was that there was a significant effect of soy isoflavone on LDL cholesterol but not total cholesterol in trials with a parallel design.

Three studies reported that they assessed adverse events. These included one case each of abdominal bloating, nicturia, recurrence of breast cancer, paraesthesia, brief recurrence of menstrual period and two cases of gastralgia.

There was no evidence of publication bias.

**Authors’ conclusions**
Ingestion of about 70mg/day of extracted soy isoflavones alone for between one and three months did not improve total and LDL cholesterol levels in menopausal women with normal cholesterol; further studies were required to verify the effects of extracted soy isoflavones.

**CRD commentary**
This review had a clear review question and inclusion criteria. The authors searched a number of relevant databases. However, the limitation to published studies reported in English, Japanese or Chinese may have led to the introduction of language and publication biases and the exclusion of some relevant studies. The authors reported using rigorous methodology at all stages of the review process. The validity assessment used an appropriate assessment tool and was used to inform the synthesis. The decision to use meta-analysis and the assessment and explorations of statistical heterogeneity appeared appropriate. However, it would have been informative if the primary analyses had been presented, instead of just the subsequent sensitivity analyses. The authors’ conclusions reflect the results of the review and appear likely to be reliable.

**Implications of the review for practice and research**
**Practice**: The authors did not state any implications for practice.

**Research**: The authors stated that further studies were required to verify the effects of extracted soy isoflavones on total and LDL cholesterol levels in types of participants other than menopausal or perimenopausal women and to assess possible adverse effects.

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This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.