Meta-analysis of natural therapies for hyperlipidemia: plant sterols and stanols versus policosanol

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CRD summary
This review found that plant sterols and stanols and policosanol reduce low-density lipoprotein cholesterol, and they are well tolerated with only mild side-effects. The authors concluded that policosanol is more effective, but this conclusion came from indirectly comparing the results from different studies. Head-to-head comparisons would be needed to confirm this assertion.

Authors' objectives
To compare the effects of plant sterols and stanols and policosanol on low-density lipoprotein (LDL) blood cholesterol levels.

Searching
MEDLINE, EMBASE, the Web of Science and the Cochrane Library were searched for literature published between January 1967 and June 2003; the search terms were given. References in relevant studies and reviews were also checked. Only peer-reviewed papers were eligible for inclusion.

Study selection
Study designs of evaluations included in the review
Only randomised double-blind, placebo-controlled trials were eligible for inclusion. Both parallel and crossover studies were included.

Specific interventions included in the review
The inclusion criteria specified studies that investigated the use of plant sterol or stanol esters equivalent to 2 g/day or greater, or policosanol at 5 mg/day or greater. The duration of treatment had to be 4 weeks or longer. Studies where the intervention of interest was used in conjunction with other antilipemic therapy were excluded. In the included studies, plant sterols or stanols were incorporated into a variety of products including margarine, mayonnaise, reduced fat spreads, salad dressing, chocolate, butter, meat, yoghurt, bread and jam. The mean daily dosages of plant stanols or sterols ranged from 2 to 8.5 g equivalent esterified dose. The mean daily dosage of policosanol, given as tablets, ranged from 5 to 30 mg. The duration of treatment ranged from 4 to 52 weeks for plant stanols or sterols, and from 4 to 104 weeks for policosanol.

Participants included in the review
The inclusion criteria stated that studies on adults, 18 years or older, were eligible for inclusion. Most of the participants in the included studies had hypercholesterolaemia, although some had normal cholesterol levels. Some participants also had diabetes, hypertension, abnormal hepatic function, atherosclerosis, coronary artery disease, or a history of myocardial infarction. The gender of the participants was not generally given. Baseline LDL levels were 4.11 mmol/L in the placebo group and 4.08 mmol/L in the treatment group for the plant stanol studies, and 4.66 mmol/L and 4.80 mmol/L, respectively, for the policosanol studies.

Outcomes assessed in the review
Only studies that reported changes in LDL levels as an outcome were eligible for inclusion. Secondary outcomes, including changes in total cholesterol, high-density lipoprotein (HDL) and triglyceride levels, were also reported, as was the LDL:HDL ratio. Tolerability and safety aspects were reported as withdrawals from treatment and details of any adverse events.

How were decisions on the relevance of primary studies made?
The authors did not state how the papers were selected for the review, or how many reviewers performed the selection.
Assessment of study quality
The quality of the studies was assessed on a number of aspects: applicability to the general population, bias and confounding, description of treatment, outcomes and follow-up, and statistical quality and interpretation. Scores of 0 to 100% were awarded. The quality of the studies was scored by the consensus of three reviewers.

Data extraction
The data were extracted by the consensus of three reviewers.

For each group in each study, the percentage change in LDL level was calculated from the baseline mean or median values to the end of study mean or median values. Missing P-values were calculated using an unpaired t-test from post-treatment means and standard deviations. In dose comparison trials, lipid reduction levels from each treatment group were combined. In dose escalation studies, the duration of treatment was considered to be total treatment time, and the final dosage and associated LDL level change were used in the analysis.

Methods of synthesis
How were the studies combined?
The mean percentage changes in LDL and other lipid levels were pooled separately for plant stanols or sterols, and for policosanol. The percentage difference was weighted by the number of participants and baseline and/or end of study variability. The Fisher method of combining P-values from individual studies was used to calculate a cumulative P-value. An unpaired t-test was used to compare net changes (treatment minus placebo) and baseline lipid parameters of plant sterol and stanol studies with those of policosanol studies.

For pooling data on withdrawals from treatment, pooled relative risks and 95% confidence intervals were calculated using the Mantel-Haenszel method. Where there were no events in a group, 0.5 was added to the tables to facilitate calculations.

How were differences between studies investigated?
Statistical heterogeneity was investigated using the chi-squared test.

Results of the review
Fifty-two trials were included: 23 on plant stanols or sterols (17 parallel trials, 1,204 participants; 6 crossover trials, 229 participants) and 29 on policosanol (2,934 participants).

The authors stated that all studies had comparatively high quality scores, between 69 and 92%.

Plant sterols or stanols.
The weighted mean change in LDL levels were greater with treatment than placebo: -11% with plant sterol or stanols versus -2.3% with placebo. Fisher's combined P-value was less than 0.0001. Compared with placebo, treatment significantly reduced total cholesterol and the LDL:HDL ratio, but there was no effect on triglycerides.

Policosanol.
The weighted mean change in LDL was greater with policosanol than with placebo: -23.7% with policosanol versus -0.1% with placebo. Fisher's combined P-value was less than 0.0001. Compared with placebo, treatment significantly reduced total cholesterol and the LDL:HDL ratio, significantly increased HDL, and caused some decrease in triglycerides.

Comparison between plant sterols or stanols and policosanol.
The net reductions in lipid levels were significantly greater with policosanol than with plant sterols or stanols: the differences observed were -14% in LDL, -9.1% in total cholesterol, -22.1% in LDL:HDL ratio and -10.9% in...
triglycerides. The net increase in HDL was also significantly greater for policosanol (12.4%).

Tolerability with both treatments was high. The pooled drop-out rate was 0% for plant sterol or stanol groups versus 0.15% for placebo, and 0.86% for policosanol groups versus 4.81% for placebo. Adverse effects were mainly mild gastrointestinal symptoms and, for policosanol, central nervous system symptoms.

Further details of results and adverse events were given in the paper.

**Authors' conclusions**
Plant sterols and stanols and policosanol are well tolerated and safe. However, policosanol was more effective at reducing LDL levels and causing other favourable changes to lipid profiles.

**CRD commentary**
The inclusion criteria for this review were clearly stated. The database search seemed appropriate, although unpublished studies were not sought. It is possible that some relevant studies were missed, potentially affecting the results of the review. The methods of the review were only partially reported. There was little information on the included studies, such as any dietary or other cointerventions that might have had an effect on the outcomes. The authors appropriately analysed studies separately according to treatment. However, the difference in effects of plant stanols and sterols versus policosanol were calculated through indirect comparisons; this method is not as reliable as direct comparisons. The authors commented that most of the policosanol studies were performed by the same group of researchers in Cuba. The authors' conclusions, especially those regarding the comparison between plant sterols or stanols and policosanol, should be read with the above comments in mind.

**Implications of the review for practice and research**
Practice: The authors stated that policosanol is a valuable addition to appropriate lifestyle changes and/or antilipaemic therapy.

Research: The authors stated that large randomised controlled trials, directly comparing different products, are needed.

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