Plant Sterols and Stanols: An Additional Therapy for Cholesterol Management

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Introduction
Coronary Heart Disease (CHD) is the single leading cause of death in the United States (6). Elevated total and low-density-lipoprotein (LDL) cholesterol increase the risk of atherosclerosis which causes CHD. Therefore, the cholesterol-lowering ability of plant sterols and stanols has been an area of intense research.

Sterols are cell membrane components. Plant sterols are similar in structure to cholesterol, but their side chains differ slightly (1,7). Both plant sterols and stanols are naturally occurring. The most common plant sterols are sitosterol, stigmasterol, and campesterol (2). Due to their lesser abundance in nature, plant stanols are often produced by hydrogenation of plant sterols (1).

Plant sterols and stanols are present in a variety of plants and plant-derived products including wood pulp, vegetables, soybeans, vegetable oils, margarine, and wheat (3,7). They have also been esterified and added in larger quantities to salad dressings, margarines, and other spreads. While the natural dietary intake of 150-450 mg/day (7) of plant sterols and stanols likely influences baseline cholesterol levels, it is the effect of larger quantities of plant sterols and stanols in enriched products that has been extensively researched. Numerous studies have demonstrated that consuming plant sterol- and stanol-fortified products lowers LDL cholesterol by about 10% (7,1). However, questions have been raised about potential adverse effects of plant sterols. This paper will analyze the effectiveness and safety of plant sterol and stanol use.

How Cholesterol is Lowered
The structural similarity of plant sterols and stanols to cholesterol enables them to compete with cholesterol for incorporation into micelles, the particles which transport lipids and cholesterol into the intestinal mucosa. This competition reduces dietary and biliary cholesterol absorption in the gastrointestinal tract (3,8).

Decreased cholesterol absorption upregulates LDL-receptor concentration (7) and therefore decreases LDL serum levels. In response to decreased absorption, the liver and other tissues increase cholesterol synthesis, but this effect is less significant than that of inhibited absorption (3,8,9). The overall effect is a reduction in LDL and total cholesterol levels without effects on HDL and triglyceride levels (1,7,10).

Similar to Cholesterol But Not Atherogenic
The similar structure of plant sterols and stanols to cholesterol raises the question about whether they, like cholesterol, could cause atherosclerosis (1). Unlike cholesterol, plant sterols and stanols are poorly absorbed and therefore do not appear to pose any risk for atherosclerosis. The only exception may be in patients with the genetic disorder phytosterolemia, which leads to increased absorption of phytosterols (plant sterols/stanols). However, the premature atherosclerosis that occurs in this disorder is believed to be related to cholesterol processing and not to increased phytosterol absorption (7).

Studies Demonstrating Lowered Cholesterol
The cholesterol-lowering ability of plant sterols has been studied since the 1950s (1,3,11-13). However, large amounts of free sterols were difficult to integrate into a daily diet. In the early
1990s, research began with sterol and stanol ester-fortified margarines and mayonnaises. Esterification made sterols and stanols soluble in these fatty products, and they could thus be delivered more easily than their free counterparts. In 1995, Miettinen et al. published a cornerstone, year-long study in which 153 people with mildly elevated cholesterol and similar dietary cholesterol intake received 3 servings/day of sitostanol ester-enriched margarine. The 2.6 g of stanol/day in the margarine lowered total and LDL cholesterol by 10 and 14%, respectively. Additionally, a reduction to 1.8 g/day had an effect comparable to 2.6 g/day. This study was controlled and randomized. However, while it was designed to be double-blind, a statistically significant number of the patients using the sitostanol margarine noticed a difference in taste—although they did not find the taste better or worse than normal margarine (14). Despite this flaw, the results of this study were striking.

A well-designed study in 1998 confirmed the cholesterol-lowering properties of stanol esters. In that study, Weststrate and Meijer performed a randomized, placebo-controlled, double-blind clinical trial with 100 subjects. They found that 1.5-3.3 g/d of sterol and stanol ester-fortified margarines significantly reduced total plasma and LDL cholesterol concentrations by 8-13% in patients with mildly elevated and normal cholesterol levels. This effect was exhibited by week 2.5 of their 3.5 week study (15). The validity of their results was further established by their efforts to confirm compliance and to assure that diet and lifestyle were similar across treatment groups.

There have been numerous other studies performed that consistently demonstrate similar cholesterol-lowering results with sterol and stanol ester-fortified spreads. An analysis of these studies showed that with doses of 2 or more g/day, reduction of LDL cholesterol ranged from 9-14% (1).

Further research has examined the ability of plant sterol ester enriched margarines to lower the cholesterol of patients on a low-fat, low-cholesterol diet. Maki et al. conducted a large-sample, randomized, double-blind, controlled study in which patients with mild to moderate primary hypercholesterolemia followed the National Cholesterol Education Program Step I diet for 9 weeks. After the first 4 weeks, researchers replaced a 50% fat spread with a control low-fat spread or with a low-fat spread enriched with either 1.1 or 2.2 g/day of sterol esters. They found that the 1.1 and 2.2 g/day groups had total cholesterol levels that were 5.2 and 6.6% lower and LDL cholesterol levels that were 7.6 and 8.1% lower, respectively, than control group levels (16). Though this study was supported by Lipton, the makers of Take Control™ sterol-enriched spread, it was well-designed and clearly demonstrated that a sterol ester-enriched spread could be a valuable addition to dietary therapy. Additionally, a similar study by Cleghorn et al. supported Maki’s results. In this study, 2 g/day of plant sterols reduced total and LDL cholesterol by 4.3% and 7.1%, respectively (17).

Two results in these studies deserve particular attention. First, Maki et al. found similar cholesterol-lowering between the groups receiving 1.1 and 2.2 g/day of sterol esters. Miettinen et al. had also seen similar cholesterol lowering effects with 1.8 and 2.6 g/day of stanol esters. In general, LDL reduction increases up to a dosage of about 1.6-2 g of sterols or stanols per day and then shows minimal increase at larger doses (2,3). Because there is conflicting data about
whether doses below 1.6 g/day achieve maximal LDL-lowering, further research should be done in this area (3).

Secondly, plant sterol esters’ effect on total and LDL cholesterol for studies in which participants followed a low-fat diet appear less compared to studies without a low-fat diet protocol. However, in a study very similar to that of Maki et al., Hallikainen and Uusitupa found total and LDL cholesterol reductions similar to that for a non-low-fat diet study at 8.1-10.6% and 8.6-13.7%, respectively (18). The reason for the discrepancy among the studies is unclear as all three studies were similar and well-designed. More research should be done in this area. However, because all of these low-fat studies do show additional cholesterol reduction with sterol esters, it would be most logical to advise that diet and sterol ester consumption be combined.

**Combined Use of Plant Sterols and Statins**
Unlike plant sterols which inhibit cholesterol absorption, statins are cholesterol-lowering drugs that inhibit cholesterol synthesis. Several studies have shown that plant sterol or stanol-enriched products in combination with statins provide LDL-lowering beyond that observed with statins alone (2). A recent study demonstrated that the effect of using a plant sterol ester in combination with statin is “equivalent to doubling the dose of statin” (4).

**Research with Low-Fat Foods**
The solubility of plantsterol and stanol esters in margarine is due to margarine’s high fat content. However, it was realized that the use of more healthful, low-fat delivery vehicles might be possible. Consequently, studies of low-fat foods enriched with nonesterified and esterified sterols and stanols have been done. Nestel et al. treated subjects with 2.4 g/day of sterol ester-enriched and nonesterified stanol-enriched cereal, bread, and margarine. This treatment reduced LDL to the same extent as in studies where margarine alone had been used (19). Mensink et al.--using low-fat yogurt--and Matti et al.--utilizing bread, meat, and jam--also found LDL reductions similar to previous margarine treatments (20,21). This research may encourage the development and marketing of more sterol and stanol-fortified products.

**How Should Plant Sterols and Stanols Be Used?**
In 2000, the FDA decided that foods with adequate plantsterol and stanol -enrichment could use a label stating that they may reduce the risk of heart disease by lowering cholesterol. To qualify, sterol-enriched products must have at least 0.65 g of sterol/serving while stanol-enriched products need 1.7 g/serving. This is based on the assumption that at least 2 servings/day will be consumed to achieve 1.3 and 3.4 g in total (22). The differing requirement conflicts with most research, which has shown plant sterols and stanols to be equally effective, and may be modified as equal effectiveness is further proven (23).

While plant sterols and stanols are beneficial, consumers must understand that they are not a substitute for other cholesterol therapy. For patients with mild hypercholesterolemia, phytosterols/stanols should be used in addition to an existing cholesterol-lowering diet and exercise program. Additionally, while the benefit from phytosterols is significant, they do not
produce the 20-60% lowering of statins (24) and are thus not a substitute for medication. Patients already using statin therapy for more severe hypercholesteroleemia should talk to their doctors before adding plant sterol products (10). Finally, while plant sterol products are safe for normocholesterolemic people, they are more useful to those with elevated cholesterol (10).

**Are There Harmful Side Effects?**
Many fat-soluble vitamins and their precursors are transported in lipoproteins. Because plant sterol and stanol-fortified products reduce cholesterol absorption, research has been done to determine if vitamin absorption is also decreased (3). Studies have shown that while most fat-soluble vitamin serum levels are unchanged with plant sterol use, alpha- and beta-carotenes, as well as lycopene levels, are decreased, and remain decreased even when normalized to reduced LDL levels (3,7,25). The impact of reduced carotene and lycopene levels is unknown (3,7). However, decreased levels can be remedied by eating one extra daily serving of a high-carotenoid food such as a tomato or carrot (5).

A number of studies have looked for phytosterol toxicity. Only at dosages of above 6 g/day were some altered enzyme activities observed (3). However, such dosages are well-beyond the point at which maximal LDL-lowering is achieved. Thus, while long-term studies of plant sterol safety are still needed, plant sterols and stanols appear to be safe at recommended doses.

**Consumer Consumption**
Despite the abundant evidence that sterol and stanol-enriched products lower cholesterol, sales of these products have been slow. The first such products, *Benecol™* and *Take Control™* spreads, hit the U.S. market in 1999. By January 2000 they had only 1.2% and 1.6%, respectively, of the U.S. margarine market (23). The FDA’s September 2000 authorization of health claim labeling has increased sales—with 2001 *Benecol* sales being $30 million compared to $17 million in 1999 (23,26). However, sales are still below initial projections. The elevated price of these margarines likely bears some of the responsibility. Additionally, the American public is “bombarded by health food claims,” (27) making it difficult for truly beneficial products to be recognized. Finally, plant sterol and stanol-enriched foods are largely limited to spreads, salad dressings, and snack bars. Expanding the types of available products would likely draw more attention to plant sterols and increase sales.

**Conclusion**
Numerous studies have generated abundant evidence to support the therapeutic use of plant sterols and stanols. More research is needed to confirm that plant sterols in combination with statins double effective statin dosage. For many people using statins, this could prevent the burden and cost of additional medication. Also, while plant sterols and stanols appear safe, long-term studies are needed to ensure that unforeseen adverse effects do not exist. Additionally, expansion of available plant sterol and stanol-enriched products, especially low-fat products, needs to occur. Research should also be carried out to investigate effective marketing strategies. Finally, the study by Maki et. al., among others, indicates that phytosterols remain highly beneficial at doses around 1 g/day (16). This suggests that the potential benefit of low levels of
phytosterols naturally present in the diet should be examined. Perhaps increases in consumption of natural phytosterol sources will turn out to be more beneficial than previously thought.

References


