Plant Sterols, Stanols, and Cardiovascular Disease

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Therapeutic lifestyle changes remain the cornerstone of therapy in lowering low-density lipoprotein cholesterol (LDL-C) and the management of cardiovascular disease (CVD). Sufficient clinical evidence exists regarding the safety and efficacy of phytosterols and phytostanols, in lowering LDL-C, in primary and secondary prevention. Their incorporation into foods like, margarine, yogurt, or beverages, is well accepted and tolerated. These will be discussed in this brief review.

Cardiovascular diseases are the leading cause of morbidity and mortality in the United States. Several epidemiological, pathological and clinical studies have shown a significant positive correlation between increased levels of plasma lipids, particularly, total cholesterol, and LDL-C, and the incidence of CVD in humans (1). The cholesterol-lowering effects of dietary plant sterols (phytosterols) have been studied since the 1950s, and that of plant stanols (phytostanols) was first reported in 1986 (2,3). Since then, phytosterols/stanols have become well-known dietary adjuncts that effectively lower cholesterol without any symptomatic side effects. To this end, the Adult Treatment Panel (ATP III) of the National Cholesterol Education Program (NCEP) recommended the addition of plant sterols/stanols (2g/day) to the diet, as part of the therapeutic lifestyle changes dietary guidelines (4). The US Food and Drug Administration also issued a health claim stating that foods containing plant stanols and stanol esters may reduce the risk of CAD (5).

Plant sterols differ from cholesterol only in the structure of their side chain, whereas saturated sterols, termed stanols, lack the Δ5 double bond in their B-ring (Figure 1). Edible oils, seeds and nuts have a high content of plant sterols, the major ones being sitosterol, campesterol, and stigmasterol. The Western daily diet contains about 100-300 mg plant sterols and 20-50 mg plant stanols. Plant sterols and stanols exert their hypocholesterolemic effects possibly by interfering with the uptake of both dietary and biliary cholesterol from the intestinal tract in humans. In vitro and in vivo studies have shown no difference between phytosterols and phytostanols in reducing cholesterol incorporation into mixed micelles, and have shown that both sterol and stanol esters, have similar cholesterol-lowering effects through micellar competition. Most published studies have reported that phytosterols /stanols exhibit their cholesterol lowering effects at the dose range of 2-3 g/day, and a single study

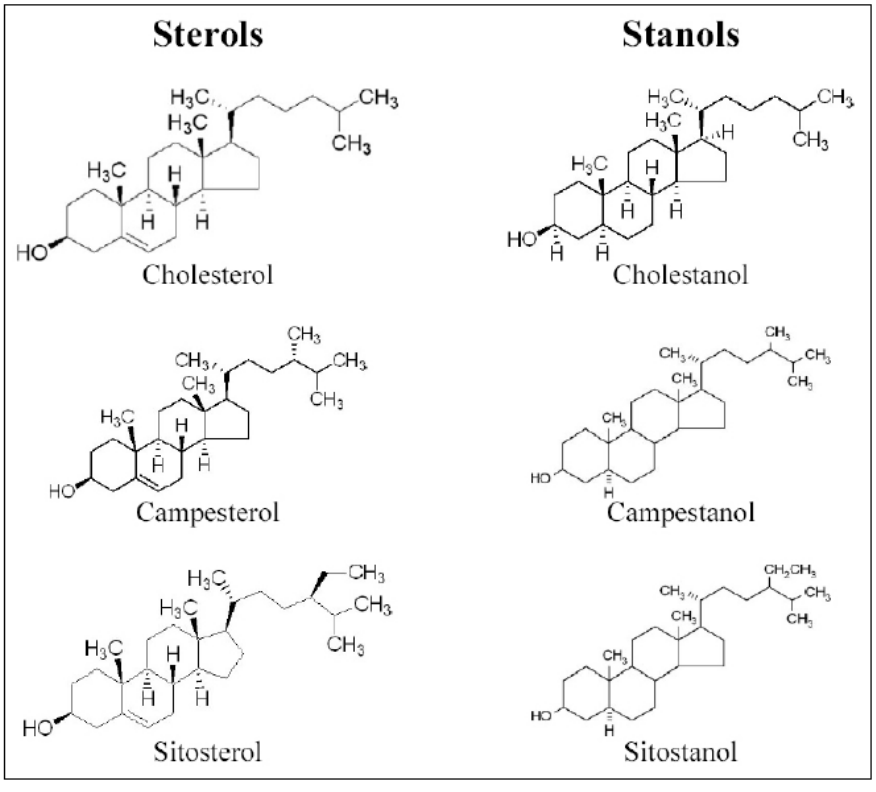

Figure 1. Structure of Plant Sterols and Stanols.

has demonstrated equivalent LDL-C lowering when administered either as single or divided doses on a daily basis (6).

The addition of plant sterols/stanols to the diet, through incorporation in fat-based foods, such as margarine, low-fat milk beverages and yogurt, has been associated with a significant reduction in serum total cholesterol and LDL-C in children, healthy normocholesterolemic and hypercholesterolemic adults, and Type 2 diabetics (7,8,9,10). Katan et al. (2003) performed a meta-analysis of 41 clinical trials, showing that the intake of 2 g/day of stanols or sterols (added to margarine, mayonnaise, olive oil, or butter), reduced LDL-C by 10-15%; intake of foods low in saturated fat and cholesterol and high in stanols or sterols, reduced LDL-C by 20%; and, additive effects were reported (16%-20% additional LDL-C lowering) by combining sterol or stanol intake with statin medication (7). In a randomized, double-blind, crossover study in 26 normocholesterolemic men, Richelle et al. (2005) reported a 60% decrease in cholesterol absorption, following a 1-week supplementation of low-fat milk-based beverage with free sterol or sterol esters (2.2 g sterol equivalents in 600 mL milk/day), compared to the control group (8). Mensink et al. (2002) have previously shown a 13.7% LDL-C lowering using esterified stanols (3 g/day) in low-fat yogurt, in 60 normocholesterolemic adults (9). In the first study examining the efficacy of plant sterols incorporated into non-fat matrices, we showed a significant 7.2% decrease in total, and a 12.4% decrease in LDL-C, in 72 mildly hypercholesterolemic subjects, following an 8-week supplementation of sterol-fortified orange juice (2 g sterol in 480 mL orange juice/day), compared to a placebo consuming sterol-free orange juice. The strategy of supplementing juices/beverages with plant sterols is very attractive, especially because it is also an excellent source of other micronutrients and antioxidants, such as ascorbate (provides the recommended daily allowance), folate, and other flavonoids; in addition to being often consumed at breakfast, it does not provide an additional source of fat, as do other phytosterol products (10). No significant effects of sterol/stanol supplementation on high-density lipoprotein (HDL) cholesterol, and triglycerides levels have been reported (9, 10). As a novel dietary strategy in lowering serum lipids and inflammation, both of which increase the risks for CAD, Jenkins et al. postulated plant sterols (1.0 g/1000 kcal), as an integral component of the "portfolio diet." The combination of phytosterols, almonds, soy protein, and viscous fibers, was shown to be equally effective as statin therapy in reducing LDL-C and C-reactive protein, a biomarker of inflammation, in hyperlipidemic adults (11). However, the active ingredient responsible for the lowering of LDL-C was not identified in this study.

An important issue that has been raised regarding the efficacy and safety of phytosterol/stanol consumption, is the concomitant decrease in plasma levels of fat-soluble vitamins, particularly, tocopherols and carotenoids, as a result of a decrease in their lipoprotein carrier molecules. A meta-analysis of 10 to 15 trials have shown that plasma levels of vitamins A, D and E, including alpha carotene and lycopene, were not affected by stanols or sterols. Beta-carotene levels underwent a decline, but it was not associated with adverse health outcomes (7). In this regard, Noakes et al. have demonstrated that an increase in consumption (≥5 servings) of high-carotenoid fruits or vegetables, like carrots, pumpkins, apricots, spinach, or broccoli, could effectively prevent the decline in plasma carotenoid concentrations accompanying phytosterol/stanol supplementation (12). In our study, with a beverage containing phytosterols (2 g/day), we failed to observe any significant reductions in vitamins E and beta carotene (unpublished data).

Yang et al. (13) showed convincingly that dietary plant sterols disrupt cholesterol homeostasis by affecting the ABC transporters, ABCG5 and ABCG8. Recently, Plat et al. also examined the mechanisms of cholesterol lowering effects of plant sterols and stanols, illustrating two distinct pathways: effects on mixed micellar composition and liver X receptor (LXR) gene activation. The authors demonstrated an increased expression of ATP binding cassette transporters (ABCA1) in

fully differentiated Caco-2 cells, which regulate cellular cholesterol levels, by transporting cholesterol back into the intestinal lumen. The LXR-activating potential of various plant sterols/stanols were positively correlated with ABCA1 mRNA expression (14).

Thus, as outlined in Table 1, plant sterols and stanols have a great potential in cardiovascular risk management, and present evidence is accumulating to promote their use for lowering LDL-C levels, as a first line of therapy as well as adjunctive therapy in patients needing a higher dose of lipid-lowering drug. Further investigations should focus on their incorporation into more commonly consumed low-fat, nutrient-dense foodstuffs, their affordability by the target population, and their effects on biomarkers of oxidative stress and inflammation, other than plasma lipids.

Table 1. Summary of cholesterol-lowering efficacy of plant sterols/stanols

- 2 g/day effectively lowers LDL-cholesterol as primary therapy
- They exert additive effects in combination with low-fat foods and statin therapy
- Are well-accepted as part of daily diet when included in margarine, butter, mayonnaise, yogurt, orange juice
- Are well-tolerated by all groups (children, type 2 diabetics, hypercholesterolemic adults)
- May act through micellar disruption

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