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Plant sterol and stanols—comparison and contrasts. Sterols versus stanols in cholesterol-lowering: is there a difference?

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1. Introduction

Sterols are ubiquitous in eukaryotic cells but absent from prokaryotes. Both animals and plants produce sterols, essential components of cell membranes. The characteristic sterol ring structure is common to cholesterol, a mainly animal product, and to all plant sterols (Fig. 1). Plant sterols (phytosterols) are naturally found in both free and esterified forms [1]. Although structurally very similar to cholesterol, they are differentiated by their degree of saturation and by their side chain configuration at the C24 position. Saturated plant sterol derivatives (termed plant stanols) are produced by the hydrogenation of sterols and are not abundant in nature. Saturation of phytosterols by commercial hydrogenation processes, including the saturation of sitosterol and campesterol at the 5 α-ring position, results in phytostanol compounds such as sitostanol and campestanol.

The terms plant sterol and phytosterol are sometimes used as generic terms to include both unsaturated sterols and saturated stanols, but they are used here to refer specifically to the unsaturated compounds. While over 40 plant sterols from seven different plant classes have been identified [2], campesterol, stigmasterol, and especially β-sitosterol are the most abundant.

Ingestion of free phytosterols, especially β-sitosterol, has been shown to reduce plasma cholesterol in both animals [1–3] and humans [4–7]. The esterified forms of phytosterols have also been used as cholesterol-lowering agents [8]. Plant sterols were first esterified and tested by Mattson [9,10]. For years research has focused on the esterified forms of plant stanols, i.e. plant stanol esters [11–20]. A recent development has been the synthetic conversion of plant sterols to their corresponding stanols followed by esterification to more fat-soluble forms. The first advantage is that the hydrogenation of sterols to their corresponding stanols makes them almost unabsorbable in the gut. Secondly, these plant stanol esters are ring-saturated analogues of common dietary sterols that have been trans-esterified with fatty acids from vegetable oils (e.g. canola) and butter. In contrast to free sterols and stanols, which are crystalline and largely insoluble, esters of the same sterols and stanols are easily dissolved in different fat-containing foodstuffs. Thus, they may be readily consumed in dietary fat, which has already been shown to be the most effective vehicle for delivering plant stanols and sterols to the small intestine [10]. The commercial esterification of plant sterols and stanols with fatty acids from vegetable oil has made it possible to produce spreads and other foods containing the desired esters.

2. Dietary sources and intakes

The presence and distribution of phytosterol compounds across plant species have been described [21,22]. In the natural world, phytosterols are found both as free sterols and as esters of such complex fatty acids as glycosides with sugar moieties and phenolic acids. Phytosterols can be found at widely varying concentrations in the fat-soluble fractions of seeds, root stems, branches, leaves and blossom. They are constituents of both edible and ornamental plants, including herbs, shrubs and trees. For example sitostanol, the hydrogenated form of sitosterol, constitutes about 20% of the total plant sterols in pine oil.

As natural constituents of the human diet, plant sterols are commonly found as minor constituents

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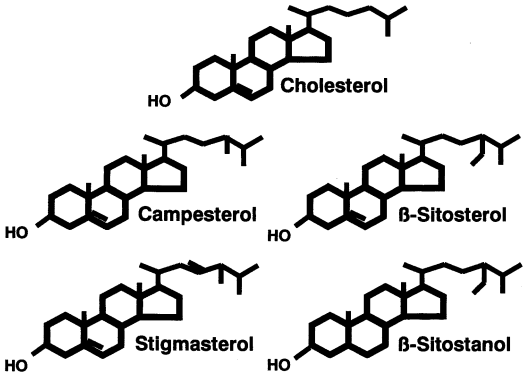

Fig. 1. Chemical structures of an animal sterol (cholesterol) and certain unsaturated (campesterol, β-sitosterol, stigmasterol) and saturated (β-sitostanol) plant sterols.

(0.1–0.5%, w/w) of edible vegetable oils [23] and of products based on vegetable oils, such as margarines (Table 1). Since fats are necessary to solubilize sterols, margarines are an ideal vehicle for them, although cream cheese and yogurt are also used. Phytosterols can also be incorporated into baked goods.

The dietary intake of phytosterols among and within different human populations varies greatly, depending on the type and amount of plant foods eaten. Although cooking oils and margarine are the main sources of plant sterols in the diet, phytosterols are also consumed in seeds, nuts, cereals and legumes. The usual intake of phytosterols in a normal Western diet has been estimated at approximately 100–300 mg of plant sterols and 20–50 mg of stanols per day [24,25]. This contrasts with a notably higher intake of plant sterols of 300–500 mg/day estimated for vegetarians and Japanese [26,27].

3. Absorption and metabolism

Since phytosterols are not synthesized by the human body, dietary consumption is the only source of plasma phytosterols. When humans consume foods rich in phytosterols, a fraction is absorbed through the gut. This increases circulating plant sterols, but their concentrations are always far lower than endogenous cholesterol. As only about 5% of ingested plant sterols are absorbed [28], plasma levels in healthy subjects are at least 100 times lower than circulating cholesterol. As well as poor absorption from the intestine, plasma phytosterols in mammalian tissue are normally kept very low due to their faster excretion by the liver than that of cholesterol [29].

Absorption rates for individual plant sterols differ markedly [29,30]. The length of the sterols' side chains affects their absorption rate. Plant sterols with the longest side chains are the least well absorbed, due to their more hydrophobic nature [30]. In contrast to plant sterols, stanols and their esters are minimally absorbed. Even if some absorption does take place, their overall effect is to reduce plant sterol serum concentrations as well as serum cholesterol levels.

Sitosterol, the most abundant phytosterol, is much less well absorbed than cholesterol ($<5\%$ vs. 20–60%). In comparison sitostanol, the 5α-saturated derivative of sitosterol, is virtually unabsorbable at $<2\%$ [31–33]. Other research has estimated the absorption rate of sitostanol to be in the range of 0–3%.

Table 1
Comparison of the physiological aspects of cholesterol, phytosterols and phytostanols

	Cholesterol	Phytosterols	Phytostanols
Dietary intake	300–500 mg/d	200–400 mg/d; vegetarians: up to 1000 mg/d	<10 mg/d
Dietary sources	Eggs, butter, dairy products, meat	Vegetable oils, nuts, seeds, grains	Coconut oil, tall oil extracts and some vegetable oils
Endogenous synthesis	Biliary cholesterol: 800–1200 mg/d	Not synthesized	Not synthesized
Rate of absorption	40–60%	$<5\%$	0.1–2%
Plasma concentration	140–320 mg/dl	0.3–1.7 mg/dl	0.3–0.6 mg/dl
Rate of excretion	40–60%	$>95\%$	$>98\%$

Curiously campestanol, which constitutes about 25% of stanol-rich margarine, appears to be well absorbed at 12–15% [30]. Small amounts of plant stanols are recovered in serum and bile following consumption of stanol esters but are effectively excreted via the bile, thereby balancing the intake-induced increase [15]. Absorbed plant sterols and stanols circulate, as does cholesterol, in lipoprotein particles in both their esterified and non-esterified forms.

The putative mechanisms by which plant sterols and stanols reduce serum cholesterol include (a) the inhibition of cholesterol absorption in the gastrointestinal tract by displacing cholesterol from micelles, (b) limiting the intestinal solubility of cholesterol, and (c) decreasing the hydrolysis of cholesterol esters in the small intestine [3]. This reduced absorption of cholesterol lowers serum cholesterol despite the compensatory increase in cholesterol synthesis which occurs in the liver and in other tissues [3,34,35].

Plant stanol consumption appears to inhibit the absorption of plant sterols as well as of cholesterol [14,15]. Recent work demonstrated that consumption of sitostanol esters decreased plasma concentrations of sitosterol in 15 mildly hypercholesterolemic subjects. The subjects replaced 50 g of their usual dietary fat with 50 g of rapeseed oil mayonnaise for 6 weeks, followed by 50 g of rapeseed oil mayonnaise containing a small dose of sitostanol ester (800 mg sitostanol/day) for 9 weeks, followed by a final 6 weeks at a higher dose of sitostanol ester (2000 mg sitostanol/day) [36].

In a crossover design with hyperlipidemic men, mean plasma campesterol and β-sitosterol concentrations increased by 71.6 and 32.5%, respectively, after consumption of 1.84 g sitosterol ester/day [8]. The same group of patients then received 1.84 g sitostanol ester/day and experienced a decline in their mean plasma campesterol and β-sitosterol levels of 27.9 and 22.7%, respectively [8]. Although consumption of the two spreads had opposing effects on the plasma concentrations of campesterol and β-sitosterol, the efficacy of the spreads in lowering cholesterol absorption and cholesterol levels remained the same.

A head-to-head comparison of the effect of sterol esters, stanol esters, and placebo on cholesterol absorption found that sterol esters reduced absorption to a slightly greater degree than stanol esters (36.2 vs. 25.9% compared with control, $P < 0.05$), although no significant difference was observed between the two diets when subjects consumed fixed diets over a 21-day period [8]. In this study, cholesterol biosynthesis was reciprocally increased by the sterol ester and stanol ester diets (53.3 vs. 37.8%, $P < 0.05$). The suppression of cholesterol absorption was the chief mechanism responsible for lowering plasma cholesterol levels, and the partial suppression of the resulting increase in cholesterol biosynthesis was a secondary action.

4. Cholesterol lowering

There is controversy regarding the efficacy of sterols versus stanols in lipid-lowering. Initial reports in rats [31] and humans [37] suggested that stanols were more effective than sterols in inhibiting cholesterol absorption and lowering plasma cholesterol. As a word of caution it must be noted that there are important difficulties in comparing studies that differ in study design, background diets, and plant sterol dosage and formulations.

However, head-to-head trials performed recently [8,19,20,38,39] have shown a similar efficacy for sterols and stanols in lowering low density lipoprotein (LDL)-cholesterol by 8–13% for amounts ranging from 1.8 to 2.5 g sterol or stanol agent/day. The major difference in circulating lipids lies in plasma sitosterol, which is elevated 0.6–1.7-fold by sterol-rich margarine and lowered by stanol-rich margarine. In another direct comparison study in men consuming prepared, fixed-food diets [8], plasma total cholesterol and LDL-cholesterol were reduced to a greater extent by sterol esters (13.4 and 12.9%, respectively), than by stanol esters (10.2 and 7.9%, respectively), or a control margarine (6.0 and 3.9%, respectively), ($P < 0.05$). There were no differences between the sterol and stanol spreads in their effects on high density lipoprotein (HDL)-cholesterol and plasma triglyceride levels.

In another investigation, sterol ester-enriched and stanol ester-enriched margarines were consumed by 34 hypercholesterolemic subjects in an outpatient crossover study [20]. Subjects consumed sequentially three rapeseed oil-based margarines—a control margarine, a stanol ester margarine, and a sterol ester margarine—for 4 weeks each with a mean daily intake of 2.01–2.04 g total plant sterols plus stanols/day. Compared with the control margarine, stanol ester-enriched and sterol ester-enriched margarines reduced serum total cholesterol by 9.2 and 7.3%, respectively ($P < 0.001$ for both). Reductions for LDL-cholesterol were 12.7 and 10.4%, respectively, ($P < 0.001$). No significant differences were found in total and LDL-cholesterol concentrations between stanol and sterol ester-enriched margarines when consumed as part of a low-fat diet.

A rather different line of research involved apoE-deficient, atherosclerotic mice. In these animals a phytosterol-enriched diet reduced the size of atherosclerotic lesions, so the concurrent elevation of plasma sitosterol did not appear to counteract the beneficial effect of lowering LDL-cholesterol. In studies of apoE-deficient mice fed 'tall oil'-derived phytosterol mixture (TODPM) compared with mice on control diets, Moghadasian et al. [40,41] demonstrated a reduction in plasma total cholesterol, a reduction in the formation of atherosclerotic lesions, and the prevention of xanthomatosis. Tall oil is a tree-derived, fat-soluble fraction of the hydrolysate produced during the wood-pulping

process. As assessed by morphometry, the atheromatous lesion area in the aortic sinuses of TODPM-treated animals was less than half that of control animals ($P < 0.0001$). A strong positive correlation ($r = 0.69$, $P < 0.01$) was found between plasma total cholesterol levels and lesion area in the aortic sinuses. Although a second study [42] failed to show regression of atherosclerotic plaque, Moghadasian et al. concluded that supplementation of a cholesterol-rich diet with TODPM significantly lowers plasma cholesterol and retards the development of atherosclerosis.

5. Plant sterols and atherogenicity: sitosterolemia

Like cholesterol, plant sterols have the potential for atherogenesis but as their plasma level is less than 1% that of cholesterol their role is insignificant [43].

The molecular mechanisms for regulating the amount of dietary cholesterol retained in the body as well as the body's ability to selectively exclude other dietary sterols are poorly understood. Studies of the rare autosomal recessive genetic disease, sitosterolemia (OMIM 210250), have shed some light on these processes. Patients suffering from sitosterolemia appear to hyperabsorb both cholesterol and plant sterols from the intestine [44–47]. Further, there are multiple defects of sterol regulation, particularly in the liver's ability to preferentially and rapidly excrete non-cholesterol sterols into bile. Consequently, people who suffer from this disease, thought to be approximately 25 people worldwide, have greatly elevated plasma plant sterol levels. Similar to hypercholesterolemic patients, they develop tendon and tuberous xanthomas, accelerated atherosclerosis, and premature coronary artery disease. The gene defects are located in the ABC transporters.

6. Conclusions

The consumption of both free and saturated plant sterols and their ester derivatives has the potential for reducing cholesterol absorption and improving circulating lipid profiles in a similar and equal manner. In general, no clear difference has been shown between the different classes of dietary spreads when consumed in identical doses, although in some cases sterols have performed better than stanols in lowering LDL-cholesterol. Both sterols and stanols would appear to be equally effective as cholesterol-lowering agents in humans [38,43,48,49].

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