

Phytosterol

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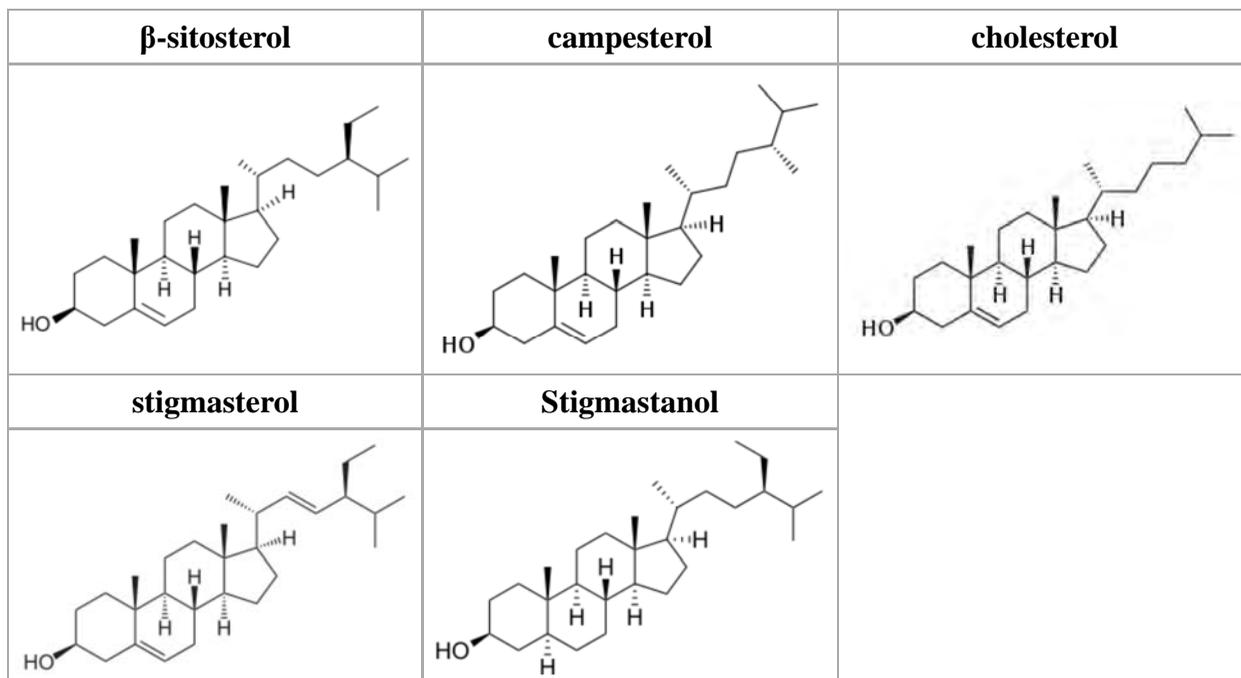
Phytosterols, which encompass plant sterols and stanols, are phytosteroids similar to cholesterol which occur in plants and vary only in carbon side chains and/or presence or absence of a double bond. Stanols are saturated sterols, having no double bonds in the sterol ring structure. More than 200 sterols and related compounds have been identified.^[1] Free phytosterols extracted from oils are insoluble in water, relatively insoluble in oil, and soluble in alcohols.

Phytosterol-enriched foods and dietary supplements have been marketed for decades. Despite well documented LDL cholesterol lowering effects, no scientifically proven evidence of any beneficial effect on cardiovascular disease (CVD) or overall mortality exists.^[2]

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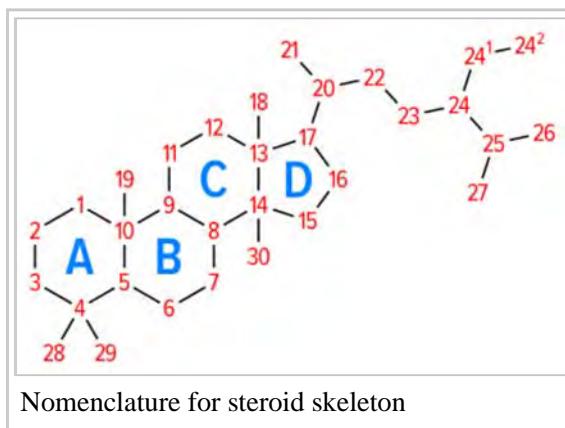
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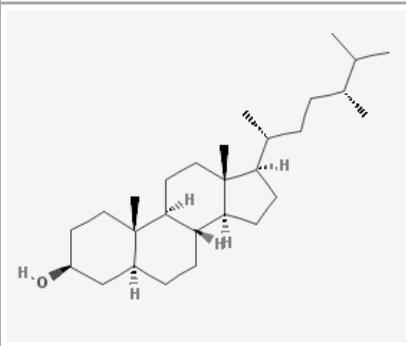
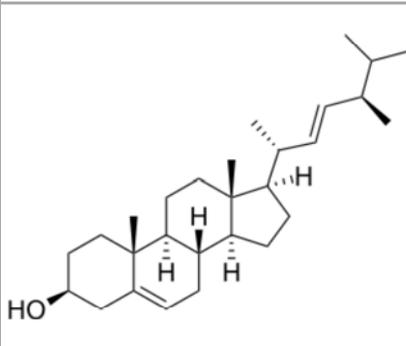
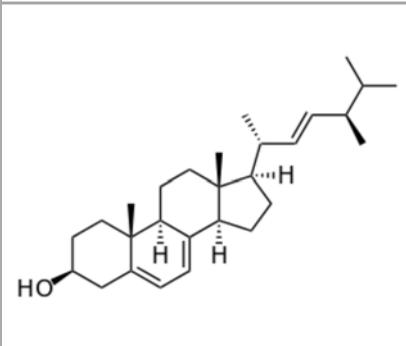
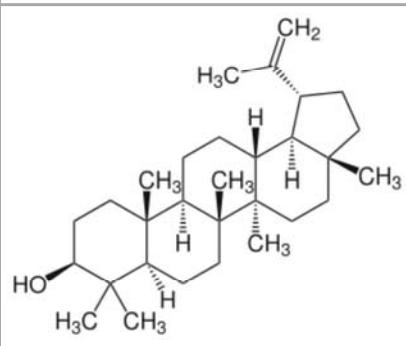
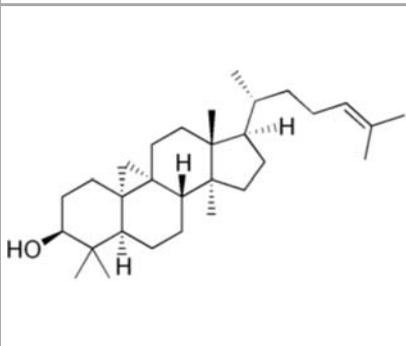
Structure



The molecule on the left is β -sitosterol. Nomenclature for steroid skeleton is on the right.

- By removing carbon 24², campesterol is obtained.
- By removing carbons 24¹ and 24², cholesterol is obtained.
- Removing a hydrogen from carbons 22 and 23 yields stigmasterol (stigma-5,22-dien-3 β -ol).
- By hydrogenating the double bond between carbons 5 and 6, β -sitostanol (Stigmastanol) is obtained.
- By hydrogenating the double bond between carbons 5 and 6 and removing carbon 24², campestanol is obtained.
- Removing carbon 24² and hydrogens from carbons 22 and 23, and inverting the stereochemistry at C-24 yields brassicasterol (ergosta-5,22-dien-3 β -ol).
- Further removal of hydrogens from carbons 7 and 8 from brassicasterol yields ergosterol (ergosta-5,7,22-trien-3 β -ol). Important: Ergosterol is not a plant sterol. Ergosterol is a component of fungal cell membranes, serving the same function in fungi that cholesterol serves in animal cells.
- Esterification of the hydroxyl group at carbon 3 with fatty/organic acids or carbohydrates results in plant sterol esters, i.e. oleates, ferulates and (acyl) glycosides.
- Actually, Lupeol is a triterpenoid, not strictly a sterol; it is not a gonane.



| campestanol | brassicasterol | ergosterol |
|---|---|--|
|  |  |  |
| lupeol | cycloartenol | |
|  |  | |

Dietary phytosterols

The richest naturally occurring sources of phytosterols are vegetable oils and products made from them. They can be present in the free form and as esters of fatty acid/cinnamic acid or as glycosides, respectively. The bound form is usually hydrolyzed in the small intestines by pancreatic enzymes.^[3] Nuts, which are rich in phytosterols, are often eaten in smaller amounts, but can still significantly contribute to total phytosterol intake. Cereal products, vegetables, fruit and berries, which are not as rich in phytosterols, may also be significant sources of phytosterols due to their higher intakes.^[4] The intake of naturally occurring phytosterols ranges between ~150–450 mg/day^[5] depending on eating habits. Specially designed vegetarian experimental diets have been produced yielding upwards of 700 mg/day.^[6] The most commonly occurring phytosterols in the human diet are β -sitosterol, campesterol and stigmasterol, which account for about 65%, 30% and 3% of diet contents, respectively.^[7] The most common plant *stanols* in the human diet are sitostanol and campestanol, which combined make up about 5% of dietary phytosterol.^[8]

Health claims

EFSA

The European Foods Safety Authority (EFSA) concluded that blood cholesterol can be reduced on average by 7 to 10.5% if a person consumes 1.5 to 2.4 grams of plant sterols and stanols per day, an effect usually established within 2–3 weeks. Longer-term studies extending up to 85 weeks showed that the cholesterol-lowering effect could be sustained.^[9] Based on this and other efficacy data, the EFSA scientific panel provided the following health advisory: “Plant sterols have been shown to lower/reduce blood cholesterol. Blood cholesterol lowering may reduce the risk of coronary heart disease”.^[10]

FDA

The FDA has approved the following claim for phytosterols: *For plant sterol esters:* (i) Foods containing at least 0.65 g per serving of plant sterol esters, eaten twice a day with meals for a daily total intake of at least 1.3 g, as part of a diet low in saturated fat and cholesterol, may reduce the risk of heart disease. A serving of [name of the food] supplies ___grams of vegetable oil sterol esters.^[11] *For plant stanol esters:* (i) Foods containing at least 1.7 g per serving of plant stanol esters, eaten twice a day with meals for a total daily intake of at least 3.4 g, as part of a diet low in saturated fat and cholesterol, may reduce the risk of heart disease. A serving of [name of the food] supplies ___grams of plant stanol esters.^[12] The FDA is currently reviewing the health claims for phytosterols.^[13] Reviewing clinical trials involving phytosterol supplementation, the FDA concluded that when consumed in the range of 1 to 3 grams in enriched foods, phytosterols resulted in statistically significant (5-15%) reductions in blood LDL cholesterol levels relative to placebo. The FDA also concluded that a daily dietary intake of 2 grams a day of phytosterols (expressed as non-esterified phytosterols) is required to demonstrate a relationship between phytosterol consumption and cholesterol lowering for reduced CVD risk.^[14]

Health Canada

Health Canada reviewed the evidence of 84 randomized controlled trials published between 1994-2007 involving phytosterol supplementation. An average 8.8% reduction in LDL-cholesterol was observed at a mean intake of 2 grams per day.^[15] Health Canada concluded that sufficient scientific evidence exists to support a relationship between phytosterol consumption and blood cholesterol lowering. Based on this evidence, Health Canada approved the following statements for qualifying foods intended for hypercholesterolemic individuals: Primary statement: "[serving size from Nutrition Facts table in metric and common household measures] of [naming the product] provides X% of the daily amount* of plant sterols shown to help reduce/lower cholesterol in adults." Two additional statements that could be used in combination or alone, adjacent to the primary statement, without any intervening printed, written or graphic material: "Plant sterols help reduce [or help lower] cholesterol." This statement when used, shall be shown in letters up to twice the size and prominence as those of the primary statement. "High cholesterol is a risk factor for heart disease." This statement when used, shall be shown in letters up to the same size and prominence as those of the primary statement.

Cholesterol lowering

The ability of phytosterols to reduce cholesterol levels was first demonstrated in humans in 1953.^{[16][17]} From 1954-82, phytosterols were subsequently marketed as a pharmaceutical under the name Cytellin as a treatment for elevated cholesterol.^[18]

Unlike the statins, where cholesterol lowering has been proven to reduce CVD risk and overall mortality under well-defined circumstances, no such effect has ever been documented with phytosterol-enriched foods or supplements.^{[2][19]} While cholesterol lowering was frequently used as a surrogate endpoint for beneficial effects on CVD, examples exist where specific medications for cholesterol lowering were found to have no significant effect on clinical endpoints, such as with ezetimibe.

Coadministration of statins with phytosterol-enriched foods increases the cholesterol-lowering effect of phytosterols, again without any proof of clinical benefit and with anecdotal evidence of potential adverse effects.^[2]

Statins work by reducing cholesterol synthesis via inhibition of the rate-limiting HMG-CoA reductase enzyme.

Phytosterols reduce cholesterol levels by competing with cholesterol absorption in the gut via one or several possible mechanisms,^{[20][21][22]} an effect that complements statins. Phytosterols further reduce cholesterol levels by about 9% to 17% in statin users.^[23] The type or dose of statin does not appear to affect the cholesterol-lowering efficacy of phytosterols.^[24]

Because of their cholesterol reducing properties, some manufacturers are using sterols or stanols as a food additive.^[25]

In preliminary research, phytosterol intake lowered triglyceride levels in people with familial hypertriglyceridemia.^[26]

Safety

Phytosterols have a long history of safe use dating back to Cytellin, the pharmaceutical preparation of phytosterols marketed in the US from 1954-82.^[18] Phytosterol esters have generally recognized as safe (GRAS) status in the US.^[27] Phytosterol-containing functional foods were subject to postlaunch monitoring after being introduced to the EU market in 2000, and no unpredicted side effects were reported.^[28]

A potential safety concern regarding phytosterol consumption is in patients with phytosterolaemia, a rare genetic disorder which results in a 50- to 100-fold increase in blood plant sterol levels and is associated with rapid development of coronary atherosclerosis. Phytosterolaemia has been linked to mutations in the ABCG5/G8 proteins which pump plant sterols out of enterocytes and hepatocytes into the lumen and bile ducts, respectively. Plant sterol levels in the blood have been shown to be positively, negatively or not associated with CVD risk, depending on the study population investigated.^{[29][30][31][32][33][34][35][36]}

The link between plant sterols and CVD or CHD risk is complicated because phytosterol levels reflect cholesterol absorption. (See Phytosterols as a marker for cholesterol absorption).

Sterol vs stanol

The equivalent ability and safety of plant sterols and plant stanols to lower cholesterol continues to be a hotly debated topic. Plant sterols and stanols, when compared head to head in clinical trials, have been shown to equally reduce cholesterol levels.^{[37][38][39]} A meta-analysis of 14 randomized, controlled trials comparing plant sterols to plant stanols directly at doses of 0.6 to 2.5 g/day showed no difference between the two forms on total cholesterol, LDL cholesterol, HDL cholesterol, or triglyceride levels.^[40] Trials looking at high doses (> 4 g/day) of plant sterols or stanols are very limited, and none have yet to be completed comparing the same high dose of plant sterol to plant stanol.

The debate regarding sterol vs. stanol safety is centered on their differing intestinal absorption and resulting plasma concentrations.^[2] Due to the extremely elevated levels of phytosterols seen in the rare genetic disorder phytosterolemia (sitosterolemia), which is associated with rapidly progressing CVD, it was hypothesized that plant sterols themselves may be atherogenic.^{[41][42]} suggested elevated plant sterol levels may be related to increased CVD risk because campesterol and total plant sterols correlated positively with cholesterol. Several other studies have suggested elevated plant sterol levels may be a risk factor for CVD.^{[33][34][35]} In these studies, though, the plant sterol levels were not as high as those seen in phytosterolemia. In phytosterolemia, the rapid development of CVD is most likely due to the improper handling of cholesterol, which is elevated and accounts for the vast majority of sterols in phytosterolemics.^[5] Because plant sterol levels actually reflect

cholesterol absorption, some have concluded elevated cholesterol absorption, not plant sterols are atherogenic or otherwise associated with CVD risk.^{[29][43]}

Research

Phytosterols are under preliminary research for their potential to inhibit lung, stomach, ovarian and breast cancers,^{[44][45]} as well as colon and prostate cancers.^[46]

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