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Phytosterols in the prevention of human pathologies

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Abstract

Coronary heart disease is a major health problem in developed countries. Many studies have shown that elevated serum concentrations of total or low-density-lipoprotein cholesterol (LDL cholesterol) are high risk factors, whereas high concentrations of high-density-lipoprotein cholesterol (HDL cholesterol) or a low LDL to HDL cholesterol ratio may protect against coronary heart disease. Plant sterols and stanols derived from vegetable oils or wood pulp have been shown to lower total and LDL cholesterol levels in humans by inhibiting cholesterol absorption from the intestine. These findings may lead to new therapeutic options to treat hypercholesterolemia. In addition, phytosterols may influence cell growth and apoptosis of tumor cells. However, they can interfere with the absorption of fat soluble vitamins and carotenoids.

Keywords

Cholesterol; Cardiovascular; Cancer; Sitosterol; Campesterol; Plant stanol

1. Introduction

A close correlation between blood cholesterol levels and heart disease has been reported in humans. Deposition of cholesterol, cholesterol esters and other lipids in the artery wall, leads to narrowing and hardening of the artery, which in turn may lead to atherosclerosis and an increased risk of forming blood clots (thrombosis).

Cholesterol is found in all animal tissues where the majority serves as a structural element in cell membrane walls, whilst the remainder is transported via the blood and acts as a precursor for other steroid based molecules such as sex hormones, steroid hormones, vitamin D or bile acids. The major sterol found in mammals is the C–27 compound cholesterol (Fig. 1).

In animals the triterpenoid alcohol lanosterol is converted into cholesterol, a process requiring the loss of three methyl groups, reduction of the side-chain double bond and generation of a $\Delta^{5,6}$ double bond in place of the $\Delta^{8,9}$ double bond (Fig. 1). Cholesterol is currently available in quantity via the brain and spinal cord of cattle as a by-product of meat

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production, and these, form one source for medicinal steroid semi-synthesis. Large quantities are also extractable from lanolin, the fatty material coating sheep's wool. Saponification of crude lanolin gives an alcohol fraction (lanolin alcohols or wool alcohols) containing about 34% cholesterol and 38% lanosterol/dihydrolanosterol. Wool alcohols are also used as an ointment base. Bile acid is obtained by purification from fresh ox bile taken from carcasses as a by-product of the meat trade. It is still important as a starting material for the semi-synthesis of other medicinal steroids being a cheap and readily accessible raw material.

Some human gallstones are almost entirely composed of cholesterol precipitated from the bile. Chenodeoxycholic acid and ursodeoxycholic acid are used to dissolve cholesterol gallstones as an alternative to surgery. By suppressing synthesis of both cholesterol and cholic acid, they contribute to removal of biliary cholesterol and consequently a gradual dissolution of gallstones, which may have formed due to supersaturation. Partial or complete dissolution requires treatment over a period of many months and is not effective for radio-opaque gallstones, which contain appreciable levels of calcium salts. Dehydrocholic acid may be used after surgery to improve biliary drainage (Fig. 2). Anion-exchange resins such as colestyramine and cholestipol are used as cholesterol-lowering drugs to bind bile acids and prevent their reabsorption. This promotes hepatic conversion of cholesterol into bile acids, increasing breakdown of low-density-lipoprotein cholesterol (LDL cholesterol).

Transport of cholesterol is facilitated by formation of lipoprotein carriers, comprising protein and phospholipid shells surrounding a core of cholesterol, in both free and esterified forms. Risk of atherosclerosis increases with increasing levels of LDL cholesterol, and is reduced with increasing levels of high-density-lipoprotein cholesterol (HDL cholesterol). Blood LDL-cholesterol levels are thus a good statistical indicators of the potential risk of a heart attack. The risks can be lessened by avoiding food rich in cholesterol. In humans dietary, cholesterol is actually a smaller contributor to LDL-cholesterol levels than is dietary saturated fat.

2. Protection from cardiovascular diseases

2.1. Cholesterol-lowering efficacy of phytosterols

Cholesterol biosynthesis may be inhibited by drug therapy using specific inhibitors of the mevalonate pathway (lovastatin and related compounds). Blood LDL-cholesterol levels may be reduced by incorporating sterol or stanol esters into the diet which reduce the absorption of cholesterol.

The main sterols in plants, are characterized by extra one carbon or two carbon substituents on the side-chain, attached at C–24. These substituent carbons are numbered 24^1 and 24^2. The widespread plant sterols campesterol and sitosterol are, respectively, 24–methyl and 24–ethyl analogues of cholesterol. Stigmasterol contains additional unsaturation in the side chain a *trans* Δ^{22} double bond, a feature seen in many plant sterols but never in mammalian ones (Fig. 3).

In fungi, ergosterol is the predominant sterol which has a β oriented 24–methyl as well as *trans* Δ^{22} double bond and additional Δ^{7} unsaturation and the most abundant sterol in brown algae is fucosterol (Fig. 4). Soybeans contain substantial amounts of sterols (about 0.2%). These include stigmasterols (about 20%), sitosterol (about 50%) that are used for the semi-synthesis of medicinal steroids and campesterol (about 20%). About 40% of the sterol content is in the free form, the remainder being combined in the form of glycosides or as esters with fatty acids.

Related materials used in a similar way are plant stanol esters (Fig. 3). Stanols are obtained by hydrogenation of plant sterols and consist mainly of sitostanol (from sitosterol and stigmasterol) and campestanol (from campesterol). These are then esterified with fatty acids. The stanols are usually transesterified with rapeseed oil which is unsaturated fatty acid.

The efficacy of dietary plant sterols in reducing cholesterol levels has led to the introduction of plant sterol esters as food additives as an aid to reducing blood levels of LDL cholesterol [1].

Plant sterols are more hydrophobic than cholesterol and have greater affinity to micelles involved in fat digestion. Thus, they can displace intestinal cholesterol from the micelles, reducing intestinal cholesterol absorption [2]. This reduction may result in a compensatory increase in endogenous cholesterol synthesis [3], higher LDL-receptor expression [4], and lower circulating LDL-cholesterol concentrations [5–7].

Sterols are forming highly stable crystals in which the hydrophilic hydroxyl groups are sequestered inside the matrix and are unavailable to solubilizing fluids. As a result, plant sterols and stanols dissolve slowly in bile salt and micelles [8], are less absorbed, their biliary excretion is faster and consequently their serum levels are very low [9]. Thus, plant sterols (such as sitosterol from soybeans) or sitostanol (a 5-α-reduced metabolite of the common plant sterol, β-sitosterol) esters are usually esterified with fatty acids to produce a fat soluble product.

Plant sterols and sitostanol lower circulating cholesterol concentrations with great variability (total and LDL-cholesterol concentrations decreased by 5–15%) [10–20].

Tall oil is the fat soluble fraction of the hydrolysate obtained from trees during the pulping process. Supplementation with 22 mg per kg body wt-1/d–1 tall oil phytosterols was effective in lowering circulating LDL-cholesterol concentrations in hypercholesterolemic subjects without changing either endogenous cholesterol synthesis or phytosterols concentrations [21]. Both sitostanol and β-sitosterol esters are proposed to reduce plasma cholesterol concentrations by competitively blocking cholesterol absorption from the intestinal lumen, displacing cholesterol from bile salt micelles, increasing bile salts excretion or hindering the cholesterol esterification rate in the intestinal mucosa [9,22–25] while stimulating [26,27], inhibiting [28] or having no effect [29] on cholesterol synthesis. Moreover, phytosterol may act on hepatic acetyl-CoA carboxylase and 7-α hydroxylase enzyme activities in animals and humans [30,31].

Although, plant sterols and stanols have no adverse effects [32], they may act on fat soluble components other than cholesterol, such as vitamins and antioxidants that might be reduced as well.

Carotenoids and tocopherols are transported by lipoproteins, like cholesterol. Thus, after consumption of plant sterols or stanols, the plasma concentrations of carotenoids and tocopherols decrease, whereas plasma concentrations of retinol, 25-hydroxy-vitamin D and vitamin K were unaffected by dietary plant sterols and stanols esters [33].

Replacement of intestinal cholesterol from the micelles is not the only mechanism by which plant sterols and stanols lower LDL cholesterol. When consumed as part of a diet low in fat and cholesterol [34,35], dietary and biliary cholesterol absorption in the intestine are both suppressed. Moreover, plant sterols and stanols esters have the potential to be effective in combination with cholesterol-lowering drugs [36].

3. Protection from colon, breast and prostate cancer

Although, it was reported that phytosterols might protect from cancer development, the mechanism of protection remains unknown although different mechanisms have been proposed [37–40]. Prostatic 5α-reductase and prostatic aromatase activities were decreased in rats supplemented with phytosterols [41,42] indicating that they may suppress prostate metabolism and growth. Sitosterol has been shown to alter tumor growth in independent studies [43–46]. The in-corporation of sitosterol in HT-29 cells membrane resulted in a significant decrease in sphingomyelin and an increase in phosphatidylcholine [43]. Thus the inhibition of tumor growth could be explained by phytosterols effect on sphingomyelin cycle and increased production of ceramide, which suggest alteration of signal transduction pathways [44,45]. It has also been observed that liver cell membrane-fluidity decreased by feeding rats with sitosterol [46]. Membrane fluidity is influenced by the lipid composition and particularly by the ratio cholesterol/phospholipids in the membrane [46–51]. Thus changes in membrane fluidity may also induce alteration in signal transduction affecting cell growth and differentiation in transformed cells. Additionally, sitosterol was shown not only to inhibit growth but also to induce apoptosis in human breast cancer cells [39]. Collectively these studies suggest that phytosterol supplementation may alter or delay tumor progression. As mentioned in the previous section, plant sterols may act on other fat soluble component, such as vitamins and antioxidants.

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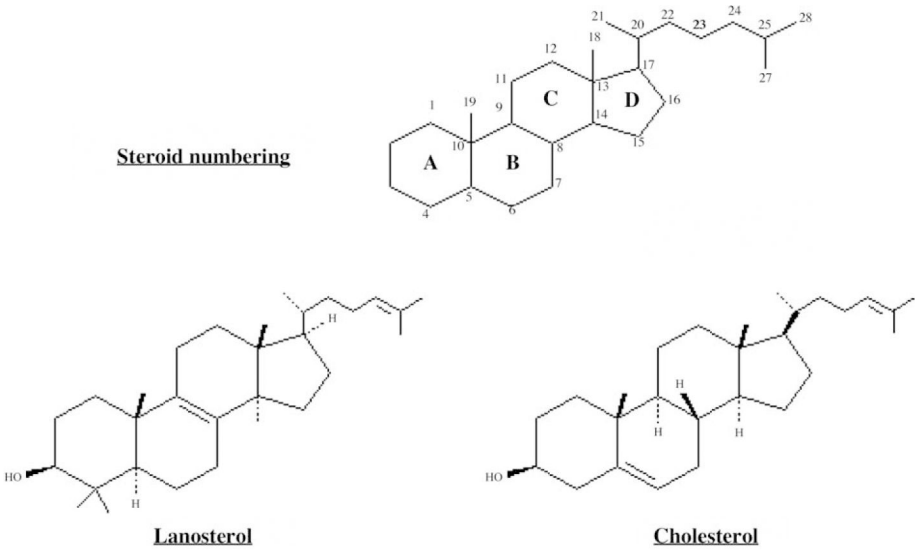

Fig. 1.
Chemical structure of cholesterol and lanosterol.

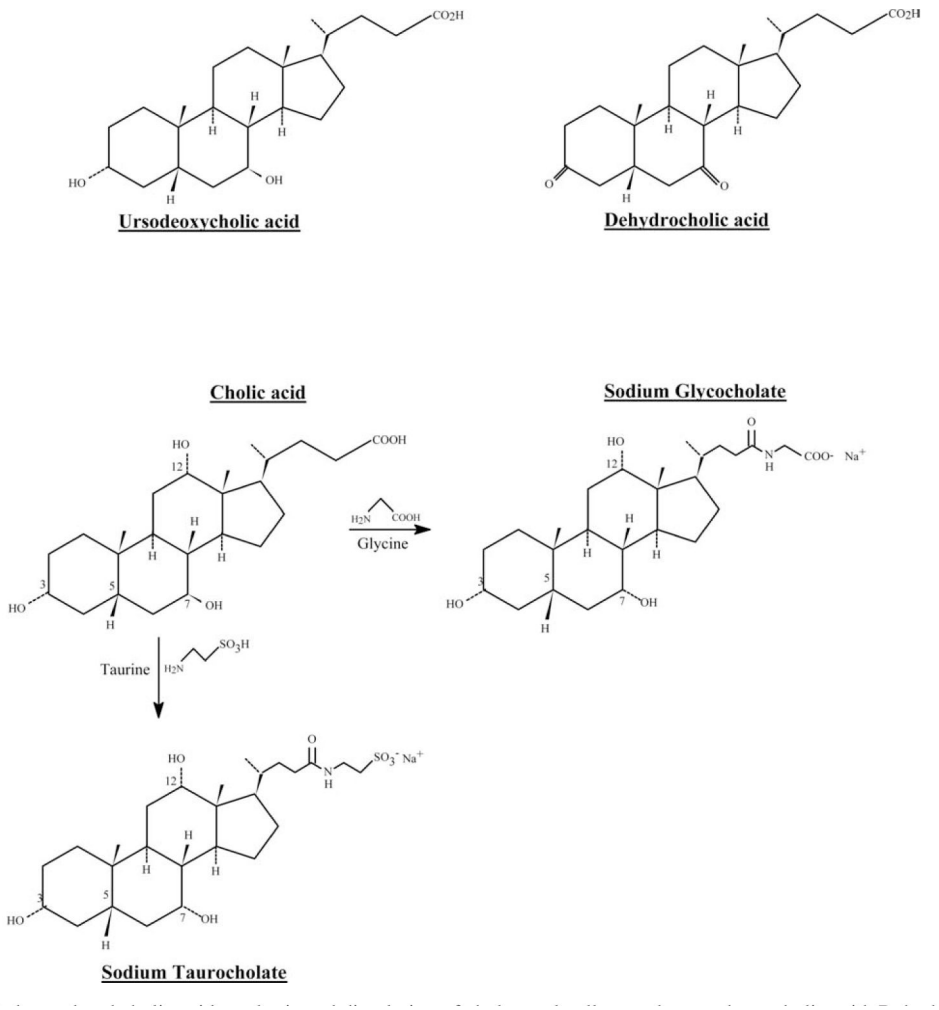

Fig. 2.

Suppression of cholesterol and cholic acid synthesis and dissolution of cholesterol gallstones by ursodeoxycholic acid. Dehydrocholic acid is used to improve biliary drainage.

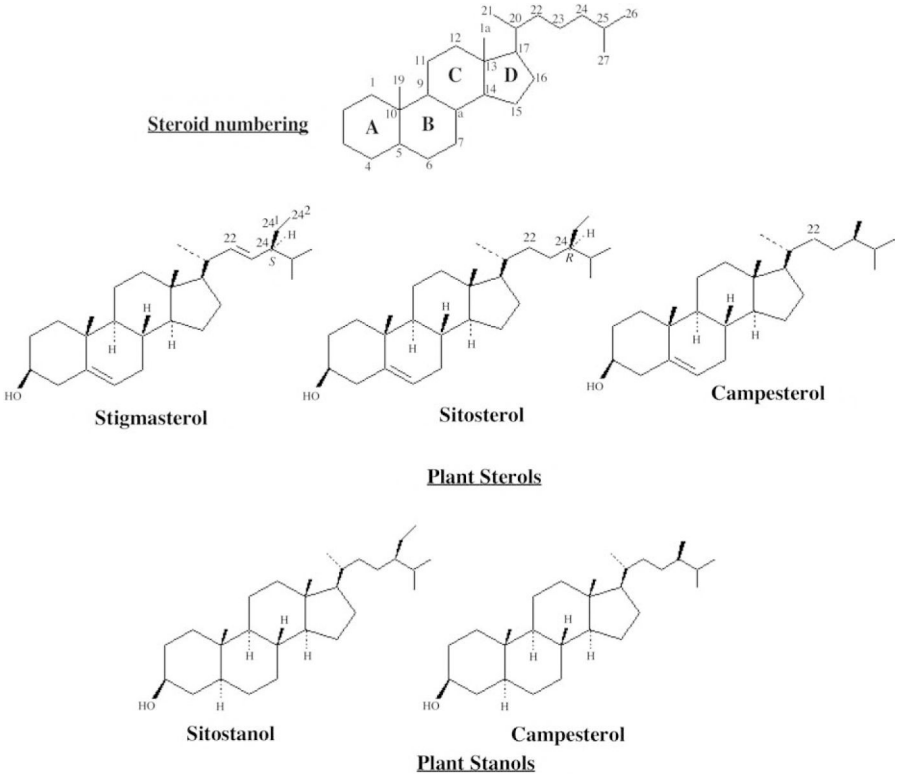

Fig. 3.
Chemical structure of phytosterols and plant stanols.

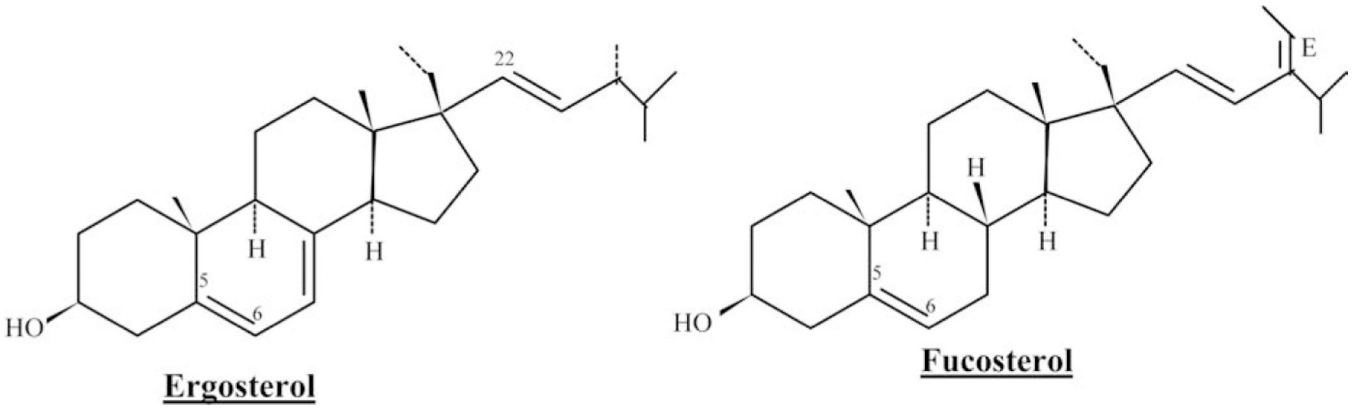

Fig. 4.
Chemical structure of fungal sterols.