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CARDIOPROTECTIVE EFFECTS OF PHYTOSTEROLS

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ABSTRACT

Foods and nutrients play a vital role in normal functioning of the body. They are helpful in maintaining the health of the individual and in reducing the risk of various diseases. Worldwide acceptance of this fact formed a recognition link between "nutrition" and "health" and the concept of "nutraceuticals" has evolved. More than any other disease, the etiology of cardiovascular disease reveals many risk factors that are amenable to nutraceutical intervention. The scientific literature shows that there are several bioactive ingredients that are present in small amounts in plants that can affect mammalian biological processes relevant to cardiovascular disease and other common human diseases. The ability of bioactive ingredients to positively influence cardiovascular risk factors should be recognized as an enormous opportunity in the treatment of a highly prevalent disease. Nutraceuticals hold promise in clinical therapy as they have the potential to significantly reduce the risk of side effects associated with drugs and pills along with reducing the global health care cost. Common ingredients that have been studied include soluble fiber (from oats and psyllium); long-chain omega-3 fatty acids; plant sterols or phytosterols; polyphenols (from dark chocolate, red wine, green tea, or extravirgin olive oil); isoflavones from soy; Chinese red-yeast rice; and probiotics from dairy products. Amongst this vast array of bioactives, there is emerging evidence indicating role of phytosterols in mitigating risk of cardiovascular disease and promoting general health and well-being. Phytosterols are cholesterol-like molecules found in all plant foods. They are absorbed only in trace amounts but inhibit the absorption of intestinal cholesterol including recirculating endogenous biliary cholesterol, a key step in cholesterol elimination. In this review, an attempt has been made to summarize some of the recent research findings on phytosterols that have beneficial effects on the heart, in order to update the practicing clinician on the benefit of using phytosterols for the management of cardiovascular diseases.

INTRODUCTION: Worldwide, the burdens of chronic diseases like cardiovascular diseases, cancers, diabetes and obesity is rapidly increasing. In 2001, cardiovascular diseases contributed approximately 59% of the 56.5 million total reported deaths in the world

and 46% of the global burden of disease¹. Cardiovascular diseases (CVD) is the name for the group of disorders of the heart and blood vessels and include hypertension (high blood pressure), coronary heart disease (heart attack), cerebrovascular disease

(stroke), heart failure, peripheral vascular disease, etc. These CVDs include hypertension, stroke, and coronary heart disease, including angina pectoris and myocardial infarction. Normalization of abnormal lipids and lipoproteins, hypertension, inhibition of platelet aggregation, and an increase in antioxidant status are believed to improve cardiovascular disease.

Majority of the CVD are preventable and controllable through dietary manipulation. Many research studies have identified a protective role of nutraceuticals against CVD². The phytosterols are arguably the most intensively studied of nutraceutical substances with regard to prevention of CVD and as a result, conclusions about them can be drawn with good scientific support. Phytosterols are plant-derived sterols that are structurally similar and functionally analogous to cholesterol in vertebrate animals. In many foods sitosterol is the most abundant form, followed by campesterol and stigmasterol.

The plant sterols are esterified in intestinal cells by creating an ester bond between a fatty acid and the sterol or stanol. Esterification makes plant sterols and stanols more fat-soluble so they are easily incorporated into fat-containing micelles in body. The various research work has shown that phytosterol feeding resulted in changes in serum cholesterol levels and dietary cholesterol absorption was noticed to be inhibited and the response to a high-cholesterol diet was attenuated³.

Structure: The chemical structure of common phytosterols is shown in Figures 1 and 2. The term "sterol" is traditionally applied by chemists to a substance with the fused cyclopentanophenanthrene ring structure of cholesterol plus an alcohol moiety and, in this sense, all the compounds in Figures 1 and 2 are sterols.

However, recent convention among nutritionists has divided phytosterols into the two categories of "sterols" or " Δ^5 -sterols," indicating a double bond at position 5, and "stanols," indicating 5α -reduction of that double bond⁴. These classes are reflected in the common names of the compounds. The sitosterol is structurally identical to sitostanol except for the double bond at position 5, and campesterol bears the same relationship to campestanol.

Reduction of the double bond to give a β -hydrogen at position 5 (facing upward from the ring system) is a common intestinal bacterial degradation product of cholesterol and plant sterols but is not generally found in foods^{5, 6}. Sterol biosynthesis and metabolism are quite different in plants and animals⁷. Cholesterol is synthesized from acetate through the straight-chain compound squalene and then cyclized to form many intermediate precursor sterols, but the final product is most often nearly pure cholesterol, and only trace amounts of related precursors are found in humans⁸. In plant cells phytosterols are also synthesized from acetate subunits through squalene, but the first cyclized product after squalene is the unique plant sterol cycloartenol (**Figure 2**).

Some foods, such as rice, contain cycloartenol or related compounds in significant amounts⁹. Plants produce a variety of final sterol products, and each species has a characteristic distribution of sterols that has sometimes been used as a chemical fingerprint for identification of food product sources. Although modifications to the sterol nucleus occur, the most common plant sterols have a nucleus that is identical to cholesterol, with changes occurring in the side chain. In foods three compounds account for most of the phytosterol mass: sitosterol (24-ethylcholesterol), campesterol (24-methylcholesterol), and stigma sterol (122-24-ethylcholesterol).

The structural similarity to cholesterol is striking, and it is difficult to separate cholesterol from phytosterols or different phytosterols from each other by physical methods unless powerful techniques such as high pressure liquid chromatography or gas chromatography involving thousands of theoretical plates are employed.

The complexity of phytosterols is increased further by steric asymmetry. Addition of alkyl groups in the side chain results in the substituted carbon becoming asymmetric¹⁰. Generally the α -configuration is more common in higher plants, whereas the β -configuration predominates in algae⁷. Stereochemistry has not generally been considered in human and animal studies of phytosterols. In animals most of the total body cholesterol is free, with a relatively small aggregate amount present as long-chain fatty acyl esters in plasma lipoproteins and specialized cells.

Plants have a more diverse variety of derivatives at the 3-position. Long-chain fatty acyl esters are present in most plants and constitute over 50% of the total sterol in foods such as corn oil¹¹. Ferrulate esters are found in appreciable quantity in many foods¹². Glycosylation occurs more actively in plants than in animals, and glycosylated phytosterols are a minor component of most foods. However, the amount is sometimes appreciable, and glycosides constitute 82% of potato phytosterols¹³. It should be emphasized that glycosidic linkages are not cleaved by the alkaline conditions used to hydrolyze sterol esters but rather require acidic hydrolysis. Phytosterol glycosides are therefore not measured by common procedures for phytosterol quantitation, and future techniques need to include both alkaline and acidic hydrolysis conditions.

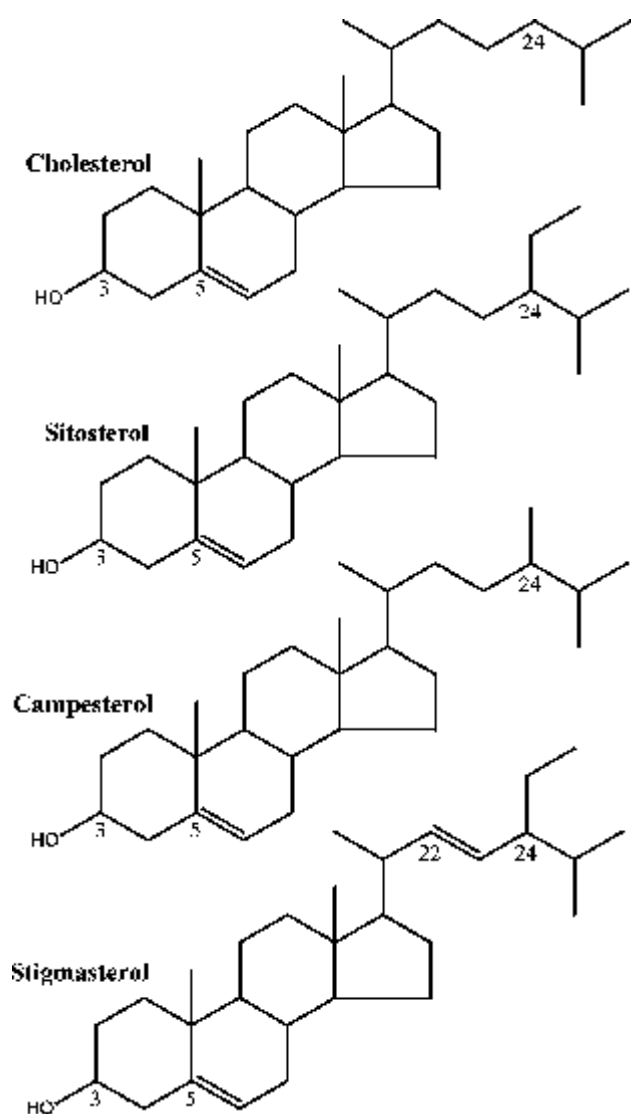


FIGURE 1: CHOLESTEROL AND COMMON Δ^5 -PHYTOSTEROLS

Source: Berger *et al.*, 2004

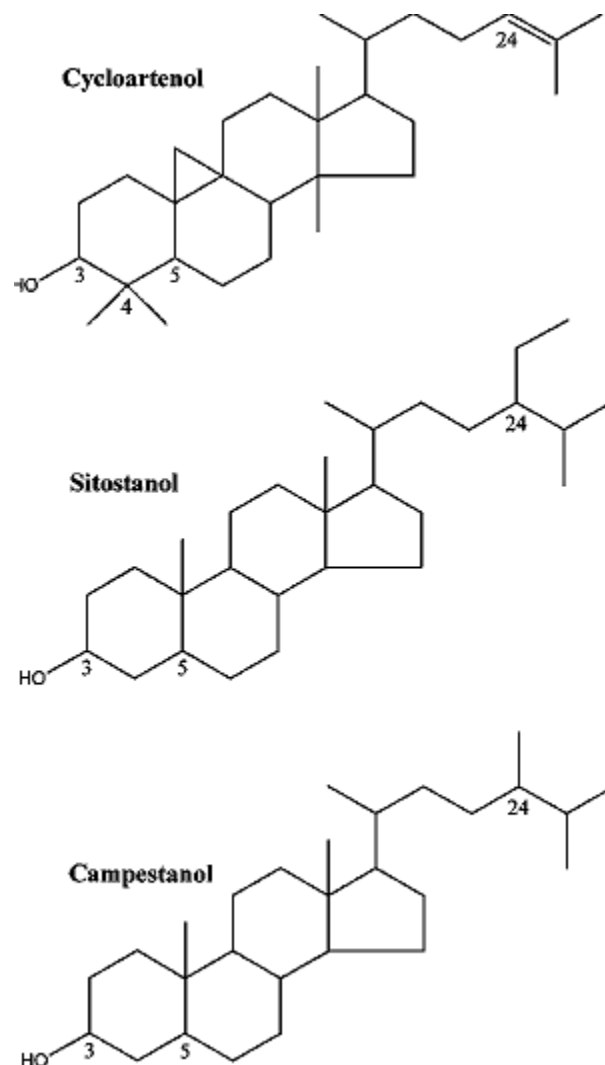


FIGURE 2: PHYTOSTANOLS WITH 5A CONFIGURATION

Source: Berger *et al.*, 2004

Sources & Foods Enriched with Plant Sterols and Plant Stanols: Phytosterols are found in all plant foods, but the highest concentrations are found in unrefined plant oils, including vegetable, nut, and olive oils¹⁴. Nuts, seeds, whole grains, and legumes are also good dietary sources of phytosterols¹⁵. The majority of clinical trials that demonstrated a cholesterol-lowering effect used plant sterol or stanol esters solubilized in fat-containing foods, such as margarine or mayonnaise¹⁶. More recent studies indicate that low-fat or even nonfat foods can effectively deliver plant sterols or stanols if they are adequately solubilized^{17, 18}.

Plant sterols or stanols added to low-fat yogurt^{19, 20-22}, low-fat milk²³⁻²⁵, low-fat cheese²⁶, dark chocolate²⁷, and orange juice^{28, 29} have been reported to lower LDL cholesterol in controlled clinical trials.

A variety of foods containing added plant sterols or stanols, including margarines, mayonnaises, vegetable oils, salad dressings, yogurt, milk, soy milk, orange juice, snack bars, and meats, are available in the U.S., Europe, Asia, Australia, and New Zealand¹⁷. A recent meta-analysis found that plant sterols/stanols added to fat spreads, mayonnaise, salad dressings, milk, or yogurt were more effective in reducing LDL cholesterol levels compared to when plant sterols/stanols were incorporated into other products, such as chocolate, orange juice, cheese, meats, and cereal bars³⁰.

Available research indicates that the maximum effective dose for lowering LDL cholesterol is about 2 g/d¹⁶ and the minimum effective dose is 0.8-1.0 g/d¹⁷. In the majority of clinical trials that demonstrated a cholesterol-lowering effect, the daily dose of plant sterols or stanols was divided among two or three meals, which may be more effective in lowering LDL cholesterol³⁰. However, consumption of the daily dose of plant sterols or stanols with a single meal has been found to lower LDL cholesterol in a few clinical trials^{19, 21, 22, 31, 32}.

TABLE 1: PHYTOSTEROL CONTENTS FROM NATURAL SOURCES

Food	Phytosterols (mg)
Wheat germ	197
Rice bran oil	162
Sesame oil	118
Corn oil	102
Canola oil	92
Peanuts	62
Wheat bran	58
Brussels sprouts	34
Rye bread	33
Macadamia nuts	33
Olive oil	22
Sunflower oil	725
Safflower oil	444
Soybean oil	221
Almonds	143
Beans	76
Corn	70
Wheat	69
Palm oil	49
Lettuce	38
Banana	16
Apple	12

SOURCE: Weirauch & Gardner 1978

Absorption and Metabolism of Dietary Phytosterols:

This mechanism of cholesterol reduction by phytoesterol has withstood the test of time and scientific scrutiny, but much remains to be learned about its details. Although varied diets typically contain similar amounts of phytosterols and cholesterol, serum phytosterol concentrations are usually several hundred times lower than serum cholesterol concentrations in humans³³. The effect of phytosterols on cholesterol absorption is incomplete. In contrast to the drug ezetimibe, which can reduce cholesterol absorption by more than 90% in animals^{34, 35}, cholesterol absorption is reduced by about 30–50%

at maximum doses of phytosterols^{36, 37, 12}. Cholesterol absorption is a very important physiological mechanism that is not limited to dietary cholesterol intake. Both dietary cholesterol (»300 mg/day) and recirculating biliary cholesterol (»1000 mg/day) mix in the intestine and are partially absorbed³⁹. Failure to reabsorb intestinal cholesterol is the principal means of cholesterol elimination from the body. Because phytosterols are not systemically absorbed, research has focused on actions that occur within the intestinal lumen. In vitro and in vivo studies of animals showed that phytosterols compete with and displace cholesterol from bile salt/phospholipid micelles, the form from which cholesterol absorption occurs⁴⁰⁻⁴².

Like cholesterol, phytosterols must be incorporated into mixed micelles before they are taken up by enterocytes. Once inside the enterocyte, systemic absorption of phytosterols is inhibited by the activity of efflux transporters, consisting of a pair of ATP-binding cassette (ABC) proteins known as ABCG5 and ABCG8⁴³. ABCG5 and ABCG8 each form one half of a transporter that secretes phytosterols and unesterified cholesterol from the enterocyte into the intestinal lumen.

Phytosterols are secreted back into the intestine by ABCG5/G8 transporters at a much greater rate than cholesterol, resulting in much lower intestinal absorption of dietary phytosterols than cholesterol. Within the enterocyte, phytosterols are not as readily esterified as cholesterol, so they are incorporated into chylomicrons at much lower concentrations. Those phytosterols that are incorporated into chylomicrons enter the circulation and are taken up by the liver.

Once inside the liver, phytosterols are rapidly secreted into bile by hepatic ABCG5/G8 transporters. Although cholesterol may also be secreted into bile, the rate of phytosterol secretion into bile is much greater than cholesterol secretion⁴⁴. Thus, the low serum concentrations of phytosterols relative to cholesterol can be explained by decreased intestinal absorption and increased excretion of phytosterols into bile. A careful analysis of the physical chemistry involved showed that sitosterol has increased affinity for biliary micelles compared with cholesterol, so sitosterol uptake by micelles is energetically favored⁴⁵.

The effect occurred in micelles containing the trihydroxy bile salt taurocholate and not with the dihydroxy bile salt glycodeoxycholate, suggesting that the distribution of bile salts present in the intestine may be important in determining the effectiveness of phytosterols in reducing cholesterol absorption. The lack of complete solubilization of cholesterol in bile salt/phospholipid micelles limits absorption is supported by studies. Further evidence of the importance of micellar solubility is the finding that the absorbability of different sterols is directly related to their equilibrium micellar concentration⁴⁵.

Even though evidence for intraluminal phytosterol action is compelling; it is also hypothesized that phytosterols may also work within the enterocyte. It is established that phytosterols are retained in the intestinal epithelium after oral ingestion^{46,47}. It is likely that phytosterols are incorporated into the plasma membrane of the enterocyte and possibly internalized as well. The latter is suggested by the finding in phytosterolemia that systemic absorption of phytosterols is associated with deficiency of the ABCG5 and ABCG8 proteins that appear to remove sterols from cells⁴⁸.

In studies in which the transport of cholesterol and sitosterol directly to intact intestinal mucosa or mucosal cells has been measured, the transfer of sitosterol has been significant, but with a rate that is 1/3 to 1/5 that of cholesterol^{49,47}. Competition of sitosterol with cholesterol for uptake into intestinal epithelium can be demonstrated at high sterol concentrations⁴². More work is needed to determine the extent of interaction of phytosterols with cholesterol within the enterocyte.

Inhibition of cholesterol absorption by the above mechanisms produces a state of relative cholesterol deficiency that is followed by upregulation of cholesterol biosynthesis and LDL receptor activity⁵⁰. After chronic phytosterol feeding whole body cholesterol biosynthesis measured by incorporation of deuterated water increased by 38–53%⁵¹ and cholesterol precursor sterol concentration in the serum, an indicator of cholesterol biosynthetic rate, rose 10–46%⁵². LDL receptor expression measured at the RNA and protein level increased 25–43% and changes in LDL levels correlated with LDL receptor expression in peripheral cells⁵².

At the level of the liver the LDL production rate was reduced by 20% and the plasma concentration of dense LDL was reduced by 22% with light LDL remaining unchanged⁵⁴. So, scientific studies have suggested that phytosterols when consumed in the diet decrease the absorption and plasma levels of cholesterol. Increasing the aggregate amount of phytosterols consumed in a variety of foods may be an important way of reducing population cholesterol levels and preventing coronary heart disease.

CONCLUSION: In the recent years, a trend has been seen in that phytosterol incorporation in practical commercial products which lower LDL cholesterol with minimal risk. Although more work needs to be done on the safety of phytosterols, it is likely the population risk of heart disease can be reduced appreciably over time by the use of more phytosterols in foods and supplements. Up to this time attention has been focused principally on the addition of phytosterol esters to fatty foods. This needs to be complemented by development of biologically active phytosterol preparations that contain minimal fat and are capable of being added to a variety of foods including nonfat foods.

However, perhaps the most important future work needs to be focused on the potential role of the lower levels of phytosterols in the natural diet and standard foods. Food databases need to include phytosterol levels to allow dietary consumption to be calculated. Clinical trials need to be done to evaluate the role of phytosterols in vegetable oils and other foods with respect to cholesterol lowering in which both the phytosterol content and the fatty acid composition of

the diet are measured and controlled. Finally, industrial manufacturing processes need to emphasize the retention of phytosterols in foods. Refining of vegetable oils can reduce the phytosterol content substantially, taking out most of the phytosterols and carotenoids from steam-refined palm oil⁵⁵ and making substantial reductions in other oils^{11,56}. With cooperation between the food industry and academia phytosterols may prove to be a useful tool to reduce cholesterol levels in large numbers of people with minimum expense and risk.

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