



APPENDIX B

Results of Medline Literature Search

Search Terms

sitosterol AND cholesterol
sitosterol AND cholesterol synthesis
sitosterol AND cholesterol absorption
plant sterols AND cholesterol synthesis
plant sterols AND cholesterol absorption
sterol ester AND cholesterol absorption
sterol ester AND cholesterol absorption
sterols

Search Results - Titles

Search Results: Sitosterol AND Cholesterol

Mora MP, et al.

Optimisation of plant sterols incorporation in human keratinocyte plasma membrane and modulation of membrane fluidity.

Chem Phys Lipids. 1999 Sep;101(2):255-65.

PMID: 10533266; UI: 20003459.

Phillips KM, et al.

Precise quantitative determination of phytosterols, stanols, and cholesterol metabolites in human serum by capillary gas-liquid chromatography.

J Chromatogr B Biomed Sci App. 1999 Sep 10;732(1):17-29.

PMID: 10517218; UI: 99444806.

Gylling H, et al.

Retinol, vitamin D, carotenes and alpha-tocopherol in serum of a moderately hypercholesterolemic population consuming sitostanol ester margarine.

Atherosclerosis. 1999 Aug;145(2):279-85.

PMID: 10488954; UI: 99417057.

Behmer ST, et al.

Phytosterol metabolism and absorption in the generalist grasshopper, *schistocerca americana*.

Arch Insect Biochem Physiol. 1999 Sep;42(1):13-25.

PMID: 10467053; UI: 99396633.

Hernandez-Pinzon I, et al.

Composition and role of tapetal lipid bodies in the biogenesis of the pollen coat of *Brassica napus*.

Planta. 1999 Jun;208(4):588-98.

PMID: 10420651; UI: 99349136.

Hashem FA, et al.

Antimicrobial components of some cruciferae plants.

Phytother Res. 1999 Jun;13(4):329-32.

PMID: 10404541; UI: 99332620.

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Bouic PJ, et al.

Plant sterols and sterolins: a review of their immune-modulating properties.

Altern Med Rev. 1999 Jun;4(3):170-7. Review.

PMID: 10383481; UI: 99316132.

Jones PJ, et al.

Cholesterol-lowering efficacy of a sitostanol-containing phytosterol mixture with a prudent diet in hyperlipidemic men.

Am J Clin Nutr. 1999 Jun;69(6):1144-50.

PMID: 10357732; UI: 99285737.

Gylling H, et al.

Cholesterol reduction by different plant stanol mixtures and with variable fat intake.

Metabolism. 1999 May;48(5):575-80.

PMID: 10337856; UI: 99268178.

Uchida K, et al.

Transformation of bile acids and sterols by clostridia (fusiform bacteria) in Wistar rats.

Lipids. 1999 Mar;34(3):269-73.

PMID: 10230721; UI: 99245752.

Warnecke D, et al.]

Cloning and functional expression of UGT genes encoding sterol glucosyltransferases from *Saccharomyces cerevisiae*, *Candida albicans*, *Pichia pastoris*, and *Dictyostelium discoideum*.

J Biol Chem. 1999 May 7;274(19):13048-59.

PMID: 10224056; UI: 99240683.

Ntanios FY, et al.

Dietary sitostanol reciprocally influences cholesterol absorption and biosynthesis in hamsters and rabbits.

Atherosclerosis. 1999 Apr;143(2):341-51.

PMID: 10217363; UI: 99231715.

Robins SJ, et al.

Delineation of a novel hepatic route for the selective transfer of unesterified sterols from high-density lipoproteins to bile: studies using the perfused rat liver.

Hepatology. 1999 May;29(5):1541-8.

PMID: 10216140; UI: 99234137.

Gylling H, et al.

Serum sterols during stanol ester feeding in a mildly hypercholesterolemic population.

J Lipid Res. 1999 Apr;40(4):593-600.

PMID: 10191283; UI: 99208729.

Garcia MD, et al.

Topical antiinflammatory activity of phytosterols isolated from *Eryngium foetidum* on chronic and acute inflammation models.

Phytother Res. 1999 Feb;13(1):78-80.

PMID: 10189959; UI: 99205957.

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Campestanol (24-methyl-5alpha-cholestan-3beta-ol) absorption and distribution in New Zealand White rabbits: effect of dietary sitostanol.

Metabolism. 1999 Mar;48(3):363-8.

PMID: 10094114; UI: 99191902.

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Hallikainen MA, et al.

Effects of 2 low-fat stanol ester-containing margarines on serum cholesterol concentrations as part of a low-fat diet in hypercholesterolemic subjects.

Am J Clin Nutr. 1999 Mar;69(3):403-10.

PMID: 10075323; UI: 99173645.

Baker VA, et al.

Safety evaluation of phytosterol esters. Part 1. Assessment of oestrogenicity using a combination of in vivo and in vitro assays.

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PMID: 10069478; UI: 99167008.

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Gender effects of tall oil versus soybean phytosterols as cholesterol-lowering agents in hamsters.

Can J Physiol Pharmacol. 1998 Jul-Aug;76(7-8):780-7.

PMID: 10030459; UI: 99153530.

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Evaluation of cholesterol absorption in rats using markers labeled with stable isotopes. Effect of complete bile diversion.

Hepatogastroenterology. 1998 Nov-Dec;45(24):2033-7.

PMID: 9951859; UI: 99135330.

Miettinen TE, et al.

The sedimentable sterols in gallstone patients before and during ursodeoxycholic acid and simvastatin treatments.

Scand J Gastroenterol. 1998 Dec;33(12):1297-302.

PMID: 9930394; UI: 99127584.

Ntanios FY, et al.

Effect of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor on sterol absorption in hypercholesterolemic subjects.

Metabolism. 1999 Jan;48(1):68-73.

PMID: 9920147; UI: 99116875.

Fujimoto Y, et al.

Stereochemistry of the reduction of 24-ethyl-desmosterol to sitosterol in tissue cultures of *Oryza sativa*.

Bioorg Med Chem Lett. 1998 Feb 3;8(3):205-8.

PMID: 9871655; UI: 99088821.

Wikstrom AC.]

[Is the Finnish "healthy margarine" food or medicine? Addition of plant sterols can lower cholesterol levels].

Lakartidningen. 1998 Nov 11;95(46):5146-8. Review. Swedish.

PMID: 9842184; UI: 99058324.

Zunin P, et al.

Sterol oxidation in infant milk formulas and milk cereals.

J Dairy Res. 1998 Nov;65(4):591-8.

PMID: 9839214; UI: 99056593.

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Del Puppo M, et al.

Serum 27-hydroxycholesterol in patients with primary biliary cirrhosis suggests alteration of cholesterol catabolism to bile acids via the acidic pathway.

J Lipid Res. 1998 Dec;39(12):2477-82.

PMID: 9831637; UI: 99051362.

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Cholesterol and its derivatives, are the principal steroids isolated from the leech species *Hirudo medicinalis*.

Comp Biochem Physiol C Pharmacol Toxicol Endocrinol. 1998

Aug;120(2):269-82.

PMID: 9827041; UI: 99044277.

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beta-Sitosterol activates the sphingomyelin cycle and induces apoptosis in LNCaP human prostate cancer cells.

Nutr Cancer. 1998;32(1):8-12.

PMID: 9824850; UI: 99042291.

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Role of ergosterol in growth inhibition of *Saccharomyces cerevisiae* by syringomycin E.

FEMS Microbiol Lett. 1998 Oct 15;167(2):215-20.

PMID: 9809422; UI: 99026950.

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Molecular organisation of amphotericin B at the air-water interface in the presence of sterols: a monolayer study.

Biochim Biophys Acta. 1998 Oct 15;1375(1-2):73-83.

PMID: 9767120; UI: 98440123.

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Overexpression of an Arabidopsis cDNA encoding a sterol-C24(1)-methyltransferase in tobacco modifies the ratio of 24-methyl cholesterol to sitosterol and is associated with growth reduction.

Plant Physiol. 1998 Oct;118(2):461-9.

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Steroidogenic acute regulatory protein (StAR) is a sterol transfer protein.

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Analysis of fecal bile acids and neutral steroids using gas-liquid chromatography.

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Nutr Rev. 1998 Aug;56(8):245-8. Review.

PMID: 9735678; UI: 98406639.

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Patel SB, et al.

Mapping a gene involved in regulating dietary cholesterol absorption. The sitosterolemia locus is found at chromosome 2p21.

J Clin Invest. 1998 Sep 1;102(5):1041-4.

PMID: 9727073; UI: 98395176.

[No authors listed]

Diet and cholesterol: foods that help.

Harv Mens Health Watch. 1998 Aug;3(1):1-3. No abstract available.

PMID: 9699474; UI: 98364630.

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Dietary sitostanol reduces plaque formation but not lecithin cholesterol acyl transferase activity in rabbits.

Atherosclerosis. 1998 May;138(1):101-10.

PMID: 9678775; UI: 98341915.

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PMID: 9650008; UI: 98313694.

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Eur J Clin Nutr. 1998 May;52(5):334-43.

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PMID: 9627377; UI: 98289066.

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Fat-modified diets influence serum concentrations of cholesterol precursors and plant sterols in hypercholesterolemic subjects.

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PMID: 9627376; UI: 98289065.

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Sitosterolemia: exclusion of genes involved in reduced cholesterol biosynthesis.

J Lipid Res. 1998 May;39(5):1055-61.

PMID: 9610773; UI: 98272304.

Koletzko B, et al.

[Hyperlipidemia in children and adolescents: diagnosis and therapy].

Schweiz Med Wochenschr. 1998 Mar 28;128(13):477-85. Review. German.

PMID: 9583098; UI: 98243933.

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Awad AB, et al.

beta-Sitosterol inhibits growth of HT-29 human colon cancer cells by activating the sphingomyelin cycle.
Anticancer Res. 1998 Jan-Feb;18(1A):471-3.
PMID: 9568122; UI: 98229542.

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Effects of variable dietary sitostanol concentrations on plasma lipid profile and phytosterol metabolism in hamsters.
Biochim Biophys Acta. 1998 Feb 23;1390(3):237-44.
PMID: 9487145; UI: 98155194.

Pakarinen MP, et al.]

Absorption, excretion, and distribution of plant sterols after proximal gut resection and autotransplantation of porcine ileum.
Lipids. 1998 Mar;33(3):267-76.
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Curri SB, et al.

[Observations on organic components of thermal mud: morphohistochemical and biochemical studies on lipid components of mud of the Terme dei Papi (Laghetto del Bagnaccio, Viterbo). Chemical bases of the interpretation of biological and therapeutic actions of thermal mud].
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Down-regulation of cholesterol biosynthesis in sitosterolemia: diminished activities of acetoacetyl-CoA thiolase, 3-hydroxy-3-methylglutaryl-CoA synthase, reductase, squalene synthase, and 7-dehydrocholesterol delta7-reductase in liver and mononuclear leukocytes.
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Competitive inhibition of hepatic sterol 27-hydroxylase by sitosterol: decreased activity in sitosterolemia.
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Weissenberg M, et al.]

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PMID: 9431673; UI: 98093797.

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Sterol utilization and metabolism by Heliothis zea.
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PMID: 9438243; UI: 98101140.

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Comparative effect of dietary sitosterol on plasma sterols and cholesterol and bile acid synthesis in a sitosterolemic homozygote and heterozygote subject.
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Regulation of early cholesterol biosynthesis in rat liver: effects of sterols, bile acids, lovastatin, and BM 15.766 on 3-hydroxy-3-methylglutaryl coenzyme A synthase and acetoacetyl coenzyme A thiolase activities.

Hepatology. 1998 Jan;27(1):154-9.

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Uusitupa MI, et al.

Lathosterol and other non-cholesterol sterols during treatment of hypercholesterolaemia with beta-glucan-rich oat bran.

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Carter CP, et al.

Genetic variation in cholesterol absorption efficiency among inbred strains of mice.

J Nutr. 1997 Jul;127(7):1344-8.

PMID: 9202089; UI: 97347450.

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Drug therapy of severe hypercholesterolemia.

Eur J Med Res. 1997 Jun 16;2(6):265-9. Review.

PMID: 9182654; UI: 97327788.

Compassi S, et al.

Comparison of cholesterol and sitosterol uptake in different brush border membrane models.

Biochemistry. 1997 Jun 3;36(22):6643-52.

PMID: 9184144; UI: 97327477.

Lutjohann D, et al.

Phytosterolaemia: diagnosis, characterization and therapeutical approaches.

Ann Med. 1997 Jun;29(3):181-4. Review.

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Jimenez-Estrada M, et al.

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PMID: 9152615; UI: 97297146.

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J Lipid Res. 1996 Aug;37(8):1776-85.

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Dietary free and esterified cholesterol absorption in cholesterol esterase (bile salt-stimulated lipase) gene-targeted mice.

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Evaluation of the use of beta-sitostanol as a nonabsorbable marker for quantifying cholesterol absorption.

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PMID: 5939905; UI: 66154721.

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Biochem J. 1965 Aug;96(2):399-403. No abstract available.

PMID: 5891218; UI: 66031544.

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The effect of beta-sitosterol on the metabolism of cholesterol and lipids in rats on a diet low in fat.
Biochem J. 1964 Aug;92(2):385-90. No abstract available.

PMID: 5891252; UI: 66032091.

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Abstracts from key articles

Food Chem Toxicol 1999 Jul;37(7):683-96

Safety evaluation of phytosterol esters. Part 3. Two-generation reproduction study in rats with phytosterol esters--a novel functional food.

Waalkens-Berendsen DH, Wolterbeek AP, Wijnands MV, Richold M, Hepburn PA
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Phytosterol esters (PE) are intended for use as a novel food ingredient with plasma cholesterol lowering activity which works by inhibiting the absorption of cholesterol from the gut. Although PE are naturally present in the normal diet, the levels are insufficiently large to ensure lowering of plasma cholesterol levels. Therefore PE may be added to spreads to achieve the desired cholesterol lowering activity. As part of an extensive programme of safety evaluation studies a two-generation reproduction study has been conducted in Wistar rats, in which the possible effect of PE on male and female reproductive performance and on the growth and development of the offspring was studied. Rats were fed diets containing PE at levels of 0, 1.6, 3.2 and 8.1% (w/w) PE over two successive generations, and a wide range of reproductive and developmental parameters, including sexual maturation parameters and oestrous cycle length, were determined. Macroscopic and microscopic examinations were conducted including a histological examination of selected organs from F1- and F2-weanlings and from F0- and F1-parental animals. Daily clinical observations did not reveal any unusual findings. In both generations, no effects of PE were observed on pup mortality (calculated on litter basis), precoital time, mating index, male and female fertility index, female fecundity index, gestation index, duration of gestation, number of females with stillborn pups, post-implantation loss and pup development. Furthermore, PE had no effect on sexual maturation parameters (preputial separation and vaginal opening) and oestrous cycle length. In addition, there were no dose-related effects on selected organs following histological examination. In conclusion, dietary administration of up to 8.1% PE (equivalent to a dose of 2.5 to 9.1 g PE/kg body weight/day, dependent on the period of the study) during two generations had no effect on reproduction of parental F0- and F1-generation Wistar rats, nor on the development of the F1- and F2-pups, nor on the sexual maturation of the F1-weanlings. Therefore, a nominal dietary PE concentration of 8.1% (equivalent to a dose of 2.5-9.1 g PE/kg body weight/day or 1.54-5.62 g phytosterol/kg body weight/day dependent on the period of the study) was considered to be the no-observed-adverse-effect level following daily oral administration of PE for two successive generations.

Curr Opin Lipidol 1999 Feb;10(1):9-14

Regulation of cholesterol metabolism by dietary plant sterols.

Miettinen TA, Gylling H
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Renewal has occurred in the use of plant sterols for the treatment of hypercholesterolemias. A novel development was to convert plant sterols to corresponding stanols and esterify them to fat soluble form. In

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contrast to the crystalline plant sterols or stanols, plant stanol esters can be easily consumed during normal food intake in soluble form in different fat-containing food constituents when they have a potent cholesterol-lowering effect, shown in normo- and hypercholesterolemic men and women without or with coronary heart disease, children and diabetes. Cholesterol lowering is approximately 10% for total and 15% for LDL cholesterol, with the respective values for stanol ester margarine (2-3 g/day stanols) being 15% and 20%. Stanol esters reduce cholesterol absorption efficiency by up to 65%, increase cholesterol elimination in feces as cholesterol itself, usually not as bile acids, and stimulate cholesterol synthesis. Serum beta-carotene level is lowered, but no fat malabsorption or lowering of serum fat soluble vitamins have been observed. In contrast to plant sterols, stanols and their esters are minimally absorbed and they reduce serum plant sterol concentrations, also preventing statin-induced increase of plant sterols. Stanol ester margarine has been included in dietary treatment of hypercholesterolemia followed by the addition of drug treatment in resistant cases.

Curr Opin Lipidol 1998 Dec,9(6):527-31

Inhibition of cholesterol absorption by plant sterols for mass intervention.

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Laboratory of Nutrition Chemistry, Faculty of Agriculture, Kyushu University, Fukuoka, Japan.

Plant sterols and stanols lower serum cholesterol by inhibiting intestinal absorption of cholesterol. Because of their safety and efficacy, their application for mass intervention is promising. The use of fatty acid esters of stanols is particularly helpful because stanols readily mix with dietary fats in this form and their hypocholesterolemic efficacy is greater than in the free form.

Food Chem Toxicol 1999 May;37(5):521-32

Safety evaluation of phytosterol esters. Part 2. Subchronic 90-day oral toxicity study on phytosterol esters--a novel functional food.

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Phytosterol esters (PE) are intended for use as a novel food ingredient, primarily in margarines and spreads as a functional component with plasma cholesterol lowering activity. Phytosterols and their esters are present naturally in vegetable oils and on average people consume 200 mg/day, but their consumption at this level is not sufficient to lower plasma cholesterol levels. Therefore, through the incorporation of PE into margarines/spreads, the intake can be increased by approximately 10-fold by consuming the PE-containing margarine/spread at normal intake levels. As part of an extensive programme of safety evaluation studies a subchronic rat toxicity study has been conducted in which groups of Alpk:AP(f)SD (Wistar derived) rats (20 males and 20 females/group) were fed diets containing PE at levels of 0, 0.16, 1.6, 3.2 and 8.1% (w/w) in the diet for 90 days. Throughout the study, clinical observations, body weights, and food and water consumption were measured. At the end of the study the rats were subjected to a full post-mortem examination, cardiac blood samples were taken for clinical pathology, selected organs were weighed, and a full tissue list was taken for subsequent histological examination. There were no treatment-related changes that were considered to be of toxicological significance. Therefore, a nominal PE concentration of 8.1% was considered to be the no-observed-adverse-effect level (NOAEL) following daily oral administration to rats for 90 days. This was equivalent to a dose of 6.6 g/kg body weight/day PE or 4.1 g/kg/day phytosterol.

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Metabolism 1998 Jun;47(6):744-50

Fat-modified diets influence serum concentrations of cholesterol precursors and plant sterols in hypercholesterolemic subjects.

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Serum noncholesterol sterols, cholesterol precursors and plant sterols, are indicators of cholesterol absorption and synthesis. Serum plant sterol concentrations correlate positively with cholesterol absorption, but have also been found to correlate with dietary unsaturated to saturated fatty acid ratios. We studied the concentration of serum noncholesterol sterols during four different fat-modified diets, (1) high-fat, saturated fat-enriched (control), (2) reduced-fat, sunflower oil-enriched (SO-enriched), (3) rapeseed oil-enriched (RO-enriched), and (4) reduced-fat, saturated fat-enriched (reduced-fat), followed for 6 months in hypercholesterolemic subjects in a parallel design. The proportion of lathosterol (micrograms per 100 mg cholesterol), a precursor of cholesterol synthesis, increased significantly ($P < .05$) in both SO-enriched (mean \pm SD 147 ± 57 v 167 ± 76 , 0 v 6 months) and RO-enriched (147 ± 54 v 157 ± 52) groups, where the reduction in low-density lipoprotein (LDL) cholesterol was also significant. The proportion of sitosterol, a plant sterol, decreased significantly in the control group (137 ± 48 v 122 ± 42), and the proportion of another plant sterol, campesterol, increased in the RO-enriched group (280 ± 141 v 333 ± 162), reflecting changes in the use of vegetable oils in these two groups rather than increased cholesterol absorption. In the whole study population, the proportion of linoleic and alpha-linolenic acid (a marker of the use of RO) in cholesterol esters (CEs) correlated ($P < .001$) with the proportion of sitosterol ($r = .43$) and campesterol ($r = .36$) in serum at the end of the study. In conclusion, serum cholesterol precursors were found to be useful indicators of cholesterol metabolism, but changes in serum plant sterols reflected dietary changes rather than cholesterol metabolism during long-term dietary intervention with fat-modified diets.

Metabolism 1999 May;48(5):575-80

Cholesterol reduction by different plant stanol mixtures and with variable fat intake.

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Our aim was to investigate (1) whether different campestanol/sitostanol mixtures in margarine differ in reducing serum cholesterol, and (2) whether sitostanol ester in butter decreases serum cholesterol and alters cholesterol absorption and metabolism. Twenty-three postmenopausal women replaced 25 g dietary fat with (1) sitostanol ester-rich (campestanol to sitostanol ratio 1:11) and (2) campestanol ester-rich (campestanol to sitostanol ratio 1:2) rapeseed oil margarine, (3) butter, and (4) sitostanol ester-rich (campestanol to sitostanol ratio 1:13) butter. The respective scheduled stanol intake was 3.18, 3.16, and 2.43 g/d. The 6-week margarine periods and, after an 8-week washout, 5-week butter periods were double-blind and in random order. Serum cholesterol precursor sterols (indicators of cholesterol synthesis) and plant sterols (indicators of cholesterol absorption) were quantified with gas-liquid chromatography (GLC). Low-density lipoprotein (LDL) cholesterol was reduced by 8% and 10% with the sitostanol and campestanol ester-rich margarines versus baseline ($P < .05$ for both) and high-density lipoprotein (HDL) cholesterol was increased by 6% and 5% ($P < .05$), so the LDL/HDL cholesterol ratio was reduced by 15% ($P < .05$ for both). Sitostanol ester-rich butter decreased LDL cholesterol 12% and the LDL/HDL cholesterol ratio 11% ($P < .05$ for both) versus the butter period. The serum proportions of plant sterols and cholestanol were similarly reduced and those of cholesterol precursor sterols were similarly increased during all periods ($P < .05$ for all). Serum proportions of sitostanol and campestanol were slightly increased, indicating that their absorption related to their dietary intake. During all stanol interventions, serum vitamin D and retinol concentrations and alpha-tocopherol to cholesterol ratios were unchanged, whereas those of alpha- and beta-carotenes were significantly reduced. We conclude that varying the campestanol to sitostanol

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ratio from 1:13 to 1:2 in margarine and in butter similarly decreased cholesterol absorption, LDL cholesterol, and the LDL/HDL cholesterol ratio such that the serum lipids became less atherogenic.

Lipids 1999 Mar;34(3):269-73

Transformation of bile acids and sterols by clostridia (fusiform bacteria) in Wistar rats.

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The effects on bile acid and sterol transformation of clostridia (fusiform bacteria), the dominant intestinal bacteria in rodents (ca. 10^{10} counts per g wet feces) were examined in Wistar rats. After inoculation of clostridia into germ-free rats and into rats previously inoculated solely with *Escherichia coli*, most of the endogenous bile acids were deconjugated, and cholic acid and chenodeoxycholic acid were 7 α -dehydroxylated to deoxycholic acid and lithocholic acid, respectively. Tauro-beta-muricholic acid, another major bile acid in rats, was deconjugated, but only part of it (ca. 30%) was transformed into hyodeoxycholic acid. Cholesterol and sitosterol were also reduced to coprostanol and sitostanol, respectively. *Escherichia coli* transformed neither bile acids nor sterols. These data suggest that clostridia play an important role in the formation of secondary bile acids and coprostanol in rats.

Hepatology 1999 May;29(5):1541-8

Delineation of a novel hepatic route for the selective transfer of unesterified sterols from high-density lipoproteins to bile: studies using the perfused rat liver.

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Cholesterol is principally excreted from the body in bile as unesterified cholesterol (UC). Using the unesterified plant sterol, sitostanol (SIT), as a nonexchangeable analog for UC, we have found that high-density lipoproteins (HDL), but not low-density lipoproteins, provide a vehicle for the direct delivery of cholesterol to bile. To determine the mechanism for preferential cholesterol transport from HDL to bile, isolated rat livers were perfused with a reconstituted HDL, made with radiolabeled unesterified SIT, UC, and cholesteryl esters (CE). Total biliary sterol secretion was independent of the concentration of HDL added to perfusions, but with increasing HDL-SIT perfused, the proportion of SIT to cholesterol in bile was linearly increased. Biliary SIT secretion was rapid (detected within 2 to 4 minutes after reconstituted HDL was added to perfusions) and was dependent on the immediate presence of SIT in the perfusate, but independent of the amount of SIT that had accumulated in the liver. The ratio of SIT to UC was seven- to ninefold greater in bile than in the liver, consistent with preferential mobilization of membrane sterols delivered from HDL. Although radiolabeled UC as well as SIT was taken up from HDL by the liver and secreted in bile, net UC uptake could not be quantitated because of both UC exchange and a sizable enrichment of HDL with UC mass that approximated the SIT removed during the passage of HDL through the liver. These results are consistent with sterol transport to bile from HDL by a direct plasma membrane pathway and by a mechanism that appears to involve substitution of unesterified (exogenous) sterol from HDL for plasma membrane UC during transport. By this process, HDL can promote reverse cholesterol transport from peripheral tissues to bile, even without an increase in biliary cholesterol secretion.

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Eur J Clin Nutr 1999 Apr;53(4):319-27

Spreads enriched with three different levels of vegetable oil sterols and the degree of cholesterol lowering in normocholesterolaemic and mildly hypercholesterolaemic subjects.

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OBJECTIVE: To investigate the dose-response relationship between cholesterol lowering and three different, relatively low intake levels of plant sterols (0.83, 1.61, 3.24 g/d) from spreads. To investigate the effects on lipid-soluble (pro)vitamins. **DESIGN:** A randomized double-blind placebo controlled balanced incomplete Latin square design using five spreads and four periods. The five study spreads included butter, a commercially available spread and three experimental spreads

fortified with three different concentrations of plant sterols. **SUBJECTS:** One hundred apparently healthy normocholesterolaemic and mildly hypercholesterolaemic volunteers participated.

INTERVENTIONS: Each subject consumed four spreads, each for a period of 3.5 week.

RESULTS: Compared to the control spread, total cholesterol decreased by 0.26 (CI: 0.15-0.36), 0.31 (CI: 0.20-0.41) and 0.35 (CI: 0.25-0.46) mmol/L, for daily consumption of 0.83, 1.61 and 3.24 g plant sterols, respectively. For LDL-cholesterol these decreases were 0.20 (CI: 0.10-0.31), 0.26 (CI: 0.15-0.36) and 0.30 (CI: 0.20-0.41). Decreases in the LDL/HDL ratio were 0.13 (CI: 0.04-0.22), 0.16 (CI: 0.07-0.24) and 0.16 (CI: 0.07-0.24) units, respectively. Differences in cholesterol reductions between the plant sterol doses consumed were not statistically significant. Plasma vitamin K1 and 25-OH-vitamin D and lipid standardized plasma lycopene and alpha-tocopherol were not affected by consumption of plant sterol enriched spreads, but lipid standardized plasma (alpha + beta)-carotene concentrations were decreased by about 11 and 19% by daily consumption of 0.83 and 3.24 g plant sterols in spread, respectively.

CONCLUSIONS: The three relatively low dosages of plant sterols had a significant cholesterol lowering effect ranging from 4.9-6.8%, 6.7-9.9% and 6.5-7.9%, for total, LDL-cholesterol and the LDL/HDL cholesterol ratio, respectively, without substantially affecting lipid soluble (pro)vitamins. No significant differences in cholesterol lowering effect between the three dosages of plant sterols could be detected. This study would support that consumption of about 1.6 g of plant sterols per day will beneficially affect plasma cholesterol concentrations without seriously affecting plasma carotenoid concentrations.

Circulation 1999 Apr 6;99(13):1733-9

Proatherogenic and antiatherogenic effects of probucol and phytosterols in apolipoprotein E-deficient mice: possible mechanisms of action.

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BACKGROUND: The effects of probucol and a phytosterol mixture (FCP-3PI) on atherosclerotic lesion formation, plasma lipoproteins, hepatic and lipoprotein lipase activities, antioxidant enzyme activities, and plasma fibrinogen were investigated in apolipoprotein E-knockout (apoE-KO) mice. **METHODS AND RESULTS:** Three groups of 8 mice were fed a diet containing 9% (wt/wt) fat (controls) or the foregoing diet supplemented with either 1% (wt/wt) probucol (the probucol group) or 2% (wt/wt) FCP-3PI (the FCP-3PI group) for 20 weeks. Compared with controls,

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atherosclerotic lesion size was 3 times greater in the probucol group, whereas it was decreased by half in the FCP-3PI group. Probucol treatment resulted in high plasma probucol concentrations, which correlated ($r=0.69$) with the lesion area. HDL cholesterol was reduced (>75%) in the probucol group and slightly increased (14%) in the FCP-3PI-treated group. Postheparin lipoprotein lipase (LPL) activity was significantly reduced in both treatment groups, but only FCP-3PI significantly decreased hepatic lipase activity. Plasma fibrinogen was increased 42% by probucol and decreased 19% by FCP-3PI relative to controls. Probucol significantly increased plasma glutathione reductase, glutathione peroxidase, and superoxide dismutase activities ($P<0.05$). In contrast to findings in apoE-KO mice, there was no probucol-induced atherosclerosis in their wild-type counterparts fed the same dose for the same period of time. CONCLUSIONS: Antiatherogenic activity of FCP-3PI in apoE-KO mice is associated with an increase in HDL cholesterol concentration along with decreases in hepatic lipase activity and plasma fibrinogen concentrations. Proatherogenic effects of probucol may be related to increased plasma fibrinogen, decreased HDL cholesterol concentrations along with decreased LPL activity, or its direct "toxicity" due to very high plasma concentration. Our studies demonstrate that the antioxidant and cholesterol-lowering properties of probucol do not prevent atherogenesis in this particular animal model.

J Lipid Res 1999 Apr;40(4):593-600

Serum sterols during stanol ester feeding in a mildly hypercholesterolemic population.

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We investigated the changes of cholesterol and non-cholesterol sterol metabolism during plant stanol ester margarine feeding in 153 hypercholesterolemic subjects. Rapeseed oil (canola oil) margarine without ($n = 51$) and with ($n = 102$) stanol (2 or 3 g/day) ester was used for 1 year. Serum sterols were analyzed with gas-liquid chromatography. The latter showed a small increase in sitostanol peak during stanol ester margarine eating. Cholestanol, campesterol, and sitosterol proportions to cholesterol were significantly reduced by 5-39% ($P < 0.05$ or less for all) by stanol esters; the higher their baseline proportions the higher were their reductions. The precursor sterol proportions were significantly increased by 10- 46%, and their high baseline levels predicted low reduction of serum cholesterol. The decrease of the scheduled stanol dose from 3 to 2 g/day after 6-month feeding increased serum cholesterol by 5% ($P < 0.001$) and serum plant sterol proportions by 8-13% ($P < 0.001$), but had no consistent effect on precursor sterols. In twelve subjects, the 12-month level of LDL cholesterol exceeded that of baseline; the non-cholesterol sterol proportions suggested that stimulated synthesis with relatively weak absorption inhibition contributed to the non-responsiveness of these subjects. In conclusion, plant stanol ester feeding lowers serum cholesterol in about 88% of subjects, decreases the non-cholesterol sterols that reflect cholesterol absorption, increases the sterols that reflect cholesterol synthesis, but also slightly increases serum plant stanols. Low synthesis and high absorption efficiency of cholesterol results in the greatest benefit from stanol ester consumption.

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Metabolism 1999 Jan;48(1):68-73

Effect of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor on sterol absorption in hypercholesterolemic subjects.

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To investigate the potential effects of high-dose 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitor on plasma phytosterol, total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and triglyceride (TG), hypercholesterolemic subjects received 40 or 80 mg/d simvastatin in a 24-week prospective clinical trial. Plasma lipid levels were analyzed enzymatically, and plasma phytosterol concentrations were determined using gas-liquid chromatography. The change in the plasma phytosterol-campesterol level was used as an indicator of cholesterol absorption in humans. Simvastatin treatment reduced plasma campesterol (-24%, $P = .017$) but did not affect circulating stigmasterol and sitosterol levels. A dose of 80 mg/d simvastatin produced a larger decrease ($P = .050$) in plasma campesterol (0.1680 mmol/L) than 40 mg/d (0.0237 mmol/L) versus baseline. There was a positive correlation between plasma campesterol and TC both before ($r = .54$, $P = .027$) and after ($r = .63$, $P = .009$) treatment. Plasma TC and TG levels did not differ between groups receiving 40 or 80 mg/d simvastatin. Simvastatin treatment reduced circulating TC, LDL-C, and TG by 40%, 50%, and 33% ($P < .007$), respectively. There was no significant effect of simvastatin on plasma HDL-C, but the HDL-C/LDL-C ratio increased 1.3-fold ($P < .0001$). In conclusion, this HMG-CoA reductase inhibitor reduces the plasma campesterol level, a marker of cholesterol absorption, which may contribute to the mechanism by which simvastatin decreases circulating cholesterol levels.

Nutr Rev 1998 Aug;56(8):245-8

Comparable efficacy of hydrogenated versus nonhydrogenated plant sterol esters on circulating cholesterol levels in humans.

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A recent study in The Netherlands compared the effects of margarine enriched with different vegetable oil sterols with margarine containing sitostanol-ester on plasma total, low-density lipoprotein (LDL), and high-density lipoprotein (HDL) cholesterol concentrations. Margarine with sterolesters from soybean oil (mainly esters from sitosterol, campesterol, and stigmasterol) was as effective as a margarine with sitostanol-ester in lowering blood total and LDL cholesterol levels without affecting HDL cholesterol levels.

Eur J Clin Nutr 1998 May;52(5):334-43

Plant sterol-enriched margarines and reduction of plasma total- and LDL-cholesterol concentrations in normocholesterolaemic and mildly hypercholesterolaemic subjects.

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OBJECTIVES: To compare effects on plasma total-, LDL-, and HDL-cholesterol concentrations of margarines enriched with different vegetable oil sterols or sitostanol-ester. **DESIGN:** A randomized double-blind placebo-controlled balanced incomplete Latin square design with five treatments and four periods of 3.5 weeks. Margarines enriched with sterols from soybean, sheanut or ricebran oil

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or with sitostanol-ester were compared to a non-enriched control margarine. Sterol intake was between 1.5-3.3 g/d. Two thirds of the soybean oil sterols were esterified to fatty acids. **SETTING:** Unilever Research Laboratory, Vlaardingen, The Netherlands. **SUBJECTS:** One hundred healthy non-obese normocholesterolaemic and mildly hypercholesterolaemic volunteers aged 45+/-12.8 y, with plasma total cholesterol levels below 8 mmol/L at entry. **MAIN OUTCOME MEASURES:** Plasma lipid, carotenoid and sterol concentrations, blood clinical chemistry and haematology, fatty acid composition of plasma cholesterylesters and food intake. **RESULTS:** Ninety-five volunteers completed the study. None of the margarines induced adverse changes in blood clinical chemistry, serum total bile acids or haematology. Plasma total- and LDL-cholesterol concentrations were significantly reduced by 8-13% (0.37-0.44 mmol/L) compared to control for margarines enriched in soybean oil sterol-esters or sitostanol-ester. No effect on HDL-cholesterol concentrations occurred. The LDL- to HDL-cholesterol ratio was reduced by 0.37 and 0.33 units for these margarines, respectively. Effects on blood lipids did not differ between normocholesterolaemic and mildly hypercholesterolaemic subjects. Plasma sitosterol and campesterol levels were significantly higher for the soybean oil sterol margarine and significantly lower for the sitostanol-ester margarine compared to control. Dietary intake was very similar across treatments. The fatty acid composition of plasma cholesterylesters confirmed the good compliance to the treatment. All sterol enriched margarines reduced lipid-standardized plasma alpha- plus beta-carotene levels. Plasma lycopene levels were also reduced but this effect was not significant for all products. **CONCLUSIONS:** A margarine with sterol-esters from soybean oil, mainly esters from sitosterol, campesterol and stigmasterol, is as effective as a margarine with sitostanol-ester in lowering blood total- and LDL-cholesterol levels without affecting HDL-cholesterol concentrations. Incorporation in edible fat containing products of such substances may substantially reduce the risk of cardiovascular disease in the population.

Metabolism 1998 Jun;47(6):751-6

Short-term administration of tall oil phytosterols improves plasma lipid profiles in subjects with different cholesterol levels.

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School of Dietetics and Human Nutrition, McGill University, Montreal, Quebec, Canada.

To assess the short-term cholesterol-lowering potential of sitostanol-containing tall oil plant sterols, 22 subjects consumed fixed-food diets over two 10-day periods with or without 21.2 mg/kg body weight/d tall oil phytosterols (sitosterol 62%, sitostanol 21%, campesterol 16%, and campestanol 1%) in a randomized crossover study design. On day 10 of each diet, plasma lipoprotein cholesterol levels, plasma phytosterol concentrations, and cholesterol biosynthesis rates were determined. Total cholesterol (TC) and low-density lipoprotein (LDL) cholesterol levels were lower ($P < .01$) after administration of tall oil phytosterol (4.7 +/- 0.3 and 3.0 +/- 0.3 mmol/L, respectively) versus placebo (5.0 +/- 0.3 and 3.2 +/- 0.3 mmol/L, respectively). Tall oil treatment had no effect on the plasma high-density lipoprotein (HDL) cholesterol level (1.1 +/- 0.1 mmol/L) versus placebo (1.1 +/- 0.1 mmol/L). Similarly, plasma triglyceride (TG) levels did not differ between tall oil (1.3 +/- 0.2 mmol/L) and placebo (1.4 +/- 0.2 mmol/L) treatments. Plasma campesterol (15.8 +/- 3.7 mmol/mol cholesterol) and sitosterol (6.0 +/- 2.1 mmol/mol cholesterol) levels were not different after tall oil treatment versus placebo treatment (15.4 +/- 2.3 and 6.4 +/- 2.0 mmol/mol cholesterol, respectively). Plasma sitostanol levels were essentially undetectable. No difference was observed in cholesterol biosynthesis between tall oil (0.045 +/- 0.004 pools/d) and placebo (0.034 +/- 0.004 pools/d) treatments; however, the effect of treatments in subjects with different cholesterol levels varied. In subjects with lower cholesterol values, the red blood cell cholesterol fractional synthesis rate (FSR) increased from 0.0291 +/- 0.0054 pools/d after placebo to 0.0509 +/- 0.0049 pools/d ($P < .05$) after phytosterol treatment. In subjects with higher cholesterol values, the red blood cell cholesterol FSR did not change significantly after treatment. These results demonstrate the short-term efficacy of tall oil plant sterols as cholesterol-lowering agents.

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Metabolism 1998 Jun;47(6):744-50

Fat-modified diets influence serum concentrations of cholesterol precursors and plant sterols in hypercholesterolemic subjects.

Sarkkinen ES, Uusitupa MI, Gylling H, Miettinen TA
Department of Clinical Nutrition, University of Kuopio, Finland.

Serum noncholesterol sterols, cholesterol precursors and plant sterols, are indicators of cholesterol absorption and synthesis. Serum plant sterol concentrations correlate positively with cholesterol absorption, but have also been found to correlate with dietary unsaturated to saturated fatty acid ratios. We studied the concentration of serum noncholesterol sterols during four different fat-modified diets, (1) high-fat, saturated fat-enriched (control), (2) reduced-fat, sunflower oil-enriched (SO-enriched), (3) rapeseed oil-enriched (RO-enriched), and (4) reduced-fat, saturated fat-enriched (reduced-fat), followed for 6 months in hypercholesterolemic subjects in a parallel design. The proportion of lathosterol (micrograms per 100 mg cholesterol), a precursor of cholesterol synthesis, increased significantly ($P < .05$) in both SO-enriched (mean \pm SD 147 \pm 57 v 167 \pm 76, 0 v 6 months) and RO-enriched (147 \pm 54 v 157 \pm 52) groups, where the reduction in low-density lipoprotein (LDL) cholesterol was also significant. The proportion of sitosterol, a plant sterol, decreased significantly in the control group (137 \pm 48 v 122 \pm 42), and the proportion of another plant sterol, campesterol, increased in the RO-enriched group (280 \pm 141 v 333 \pm 162), reflecting changes in the use of vegetable oils in these two groups rather than increased cholesterol absorption. In the whole study population, the proportion of linoleic and alpha-linolenic acid (a marker of the use of RO) in cholesterol esters (CEs) correlated ($P < .001$) with the proportion of sitosterol ($r = .43$) and campesterol ($r = .36$) in serum at the end of the study. In conclusion, serum cholesterol precursors were found to be useful indicators of cholesterol metabolism, but changes in serum plant sterols reflected dietary changes rather than cholesterol metabolism during long-term dietary intervention with fat-modified diets.

Lipids 1998 Mar;33(3):267-76

Absorption, excretion, and distribution of plant sterols after proximal gut resection and autotransplantation of porcine ileum.

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Contribution of different gut segments to plant sterol absorption, adaptation of plant sterol absorption after partial small bowel resection, and effects of gut transplantation (necessitates extrinsic autonomic denervation and lymphatic disruption) on plant sterol biodynamics are unclear. We studied the consequences of massive proximal small bowel resection and autotransplantation of the remaining ileum on the adaptive absorption and biodynamics of plant sterols. Dietary, fecal, biliary, hepatic and plasma plant sterols, fecal elimination and absorption of cholesterol, small bowel morphology, and intestinal transit were determined before ($n = 5$) and at 4, 8, and 14 wk after resection of the proximal 75% of the jejunioileum ($n = 15$) and autotransplantation of the remaining ileum ($n = 15$) or transection ($n = 5$). Proximal gut resection significantly reduced cholesterol absorption efficiency; percentage absorption and biliary secretion of plant sterols; plasma, biliary and hepatic campesterol-to-cholesterol proportions; and sitosterol proportions in plasma and bile. Autotransplantation of the remaining ileum further significantly decreased cholesterol absorption efficiency; percentage absorption and biliary secretion of campesterol; campesterol proportions in plasma, bile and liver; and plasma proportions of sitosterol while increasing fecal excretion of neutral and acidic steroids. Plasma proportions of the two plant sterols, but absorption of just campesterol, were gradually improved with increasing cholesterol absorption and villus height after proximal gut resection; the same result was observed to a lesser degree after ileal autotransplantation. In addition, significant

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positive correlations were found between percentage cholesterol and campesterol absorption and the plasma plant sterol proportions in both proximal resection groups, between campesterol absorption and ileal villus height in the resection group, and between campesterol absorption and intestinal transit time in the autotransplantation group. In conclusion, plasma campesterol and sitosterol closely reflect absorption of cholesterol and plant sterols from intact and autotransplanted ileum during adaptation to proximal gut resection. A loss of proximal gut absorptive surface impairs cholesterol and campesterol absorption more than sitosterol absorption, the latter being apparently less dependent on available jejunal villus surface area.

J Am Coll Nutr 1997 Dec;16(6):605-13

Comparative effect of dietary sitosterol on plasma sterols and cholesterol and bile acid synthesis in a sitosterolemic homozygote and heterozygote subject.

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Laboratory of Biochemical Genetics and Metabolism, Rockefeller University, New York, New York, USA.

OBJECTIVE: Sitosterolemia is a genetic disorder characterized by an increased plasma plant sterol concentration due to enhanced sterol absorption coupled with reduced steroid excretion. The purpose of the present investigation was two-fold; first to assess the effects of a "basal" low sitosterol metabolic diet on plasma sterols and sterol balance, and, secondly, to quantify the relative influence of graduated increase in dietary sitosterol intake on a metabolic diet in a sitosterolemic homozygote, obligate heterozygote, and controls. **METHODS:** Patients were studied under strict metabolic conditions and fed a "basal" 30% fat, low-sitosterol (33 mg per 2000 kcal) diet. The level of dietary sitosterol was increased by addition of oils and resulted in final dietary sitosterol intakes of 1.8 mg/kg, 2.6 mg/kg and 3.5 mg/kg/day intakes of dietary sitosterol in the homozygote. These sitosterol dosages were selected based on sitosterol intakes equivalent to 2.6 mg/kg/day in the average American diet. Plasma cholesterol, sitosterol, and apolipoprotein A were measured, and stool collections assayed for sterol balance. **RESULTS:** Fecal sterol excretion and cholesterol synthesis were depressed markedly by 50% in the homozygote compared to the heterozygous parent, whereas plasma sitosterol levels were increased over 50-fold. When the sitosterol content of the diet was increased three-fold and dietary cholesterol was maintained in the homozygous and hypercholesterolemic control, plasma levels did not increase in the homozygote. Plasma cholesterol and sitosterol levels were unaffected in the hypercholesterolemic control. **CONCLUSIONS:** Plasma sterol levels remained elevated with the dietary sitosterol changes in the sitosterolemic homozygote. These findings were associated with a low fecal sterol excretion rate and depressed endogenous cholesterol synthesis. In this sitosterolemic patient, a very low sitosterol diet to curtail sterol input was of minimal therapeutic benefit. These results have important implications regarding the selection of therapy for this patient under these experimental conditions, but cannot be generalized to other homozygotes.

Biochemistry 1997 Jun 3;36(22):6643-52

Comparison of cholesterol and sitosterol uptake in different brush border membrane models.

Compassi S, Werder M, Weber FE, Boffelli D, Hauser H, Schulthess G

Laboratorium für Biochemie, Eidgenössische Technische Hochschule Zurich, ETH Zentrum, Switzerland.

(I) There is little discrimination between cholesterol and the plant sterol sitosterol in the uptake at the brush border membrane (BBM). (II) This difference cannot account for the marked discrimination between cholesterol and sitosterol observed in the absorption of these two sterols

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by the small-intestinal epithelium. (III) This discrimination occurs during intracellular processing involving the esterification and incorporation into lipoprotein particles of the two sterols. This conclusion is based on a comparative study of sterol uptake by brush border membrane vesicles (BBMV) and sterol absorption by Caco-2 cells. (IV) The uptake of sitosterol by the BBM is energy-independent and facilitated in a manner analogous to cholesterol uptake [Thurnhofer, H., & Hauser, H. (1990a) *Biochemistry* 29, 2142-2148]. (V) The rate of cholesterol and sitosterol uptake by BBMV from both mixed bile salt micelles and small unilamellar vesicles (SUV) as the donor is directly proportional to the sterol content of the donor. (VI) The pseudo-first-order rate constants k_1 for sterol uptake from SUV are independent of the sterol content up to 10-20 mol %. Above that, competition between the two sterols leads to a reduction of the k_1 values.

Digestion 1996;57(2):83-9

Serum cholesterol, cholesterol precursors and plant sterols in different inflammatory bowel diseases.

Hakala K, Vuoristo M, Miettinen TA

Division of Internal Medicine, University of Helsinki, Finland.

The role of cholestasis and ileal dysfunction on sterol metabolism was studied in 79 patients with inflammatory bowel diseases (IBDs) and in 23 irritable bowel syndrome (IBS) controls by determining serum sterol/cholesterol proportions. The sterols included cholesterol precursors (delta 8-cholestenol, desmosterol and lathosterol), markers of cholesterol synthesis, cholestanol and plant sterols (campesterol and sitosterol), markers of cholesterol absorption and biliary secretion. The IBD patients were subgrouped into distal ulcerative colitis (dUC, n = 21), pancolitis (pUC, n = 29), ileal Crohn's disease (iCD, n = 20) and colonic Crohn's disease (cCD, n = 9). The cholestanol proportions were increased in the 3 colonic IBD groups, up to two times in cCD patients and seven times in a case with clinically overt primary sclerosing cholangitis, but were within the control IBS levels in the patients with iCD. The sitosterol, but not campesterol, proportion was significantly increased only in the pUC group. In the iCD group only the serum precursor sterol proportions, especially those for delta 8-cholestenol and lathosterol, were elevated probably due to ileal dysfunction induced bile acid malabsorption and compensatorily increased cholesterol synthesis. In conclusion, the findings suggest that the increased cholestanol proportion in colonic IBD is determined mainly by impaired biliary elimination of this sterol, while in ileal affision the dominating change in sterol balance is activated cholesterol synthesis. Thus increased serum cholestanol is a novel finding in colonic IBD, apparently indicating the presence of subclinical cholestasis in a marked number (20-50%) of IBD patients.

Hepatology 1995 May;21(5):1261-8

Serum cholestanol, cholesterol precursors, and plant sterols during placebo-controlled treatment of primary biliary cirrhosis with ursodeoxycholic acid or colchicine.

Miettinen TA, Farkkila M, Vuoristo M, Karvonen AL, Leino R, Lehtola J, Friman C, Seppala K, Tuominen J

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A randomized placebo-controlled 2-year study was performed in 69 patients with primary biliary cirrhosis (PBC) on serum lipids during ursodeoxycholic acid (URSO) and colchicine treatments. In addition to serum bilirubin and alkaline phosphatase (AFOS), two variables considered to reflect liver function, serum lipoproteins, cholesterol precursors (squalene, delta 8-cholestenol, lathosterol and desmosterol), markers of cholesterol synthesis, cholestanol and plant sterols (campesterol and sitosterol), markers of liver function and cholesterol absorption, were studied before and during the treatments. Serum bilirubin was inconsistently improved by URSO,

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whereas improvement of AFOS values was better by URSO than colchicine, especially in patients with initially more advanced PBC. Serum total cholesterol was reduced by both drugs, very low-density lipoprotein (VLDL) and high-density lipoprotein (HDL) cholesterol by URSO. Cholesterol precursor sterols were increased by both URSO and colchicine mainly in patients with initially less severe PBC. On the other hand, the cholestanol values were markedly increased initially, and the values were related to bilirubin during the 2-year period, were further increased in the placebo group, and reduced in the URSO and colchicine groups, so that the improvement was highest in the URSO-treated patients with the severe form of PBC. The increase of the serum plant sterols, particularly that of sitosterol, was retarded by the two drugs so that the campesterol/sitosterol ratio, which was related to serum bilirubin, was increased especially in the cases with initially more advanced PBC.

J Pediatr 1993 Feb;122(2):292-6

Treatment of severe familial hypercholesterolemia in childhood with sitosterol and sitostanol.

Becker M, Staab D, Von Bergmann K

Department of Pediatrics, University of Bonn, Federal Republic of Germany.

This study was undertaken to compare the ability of two plant sterols to reduce serum levels of lipids and to compare their mechanism of action in nine children with severe familial hypercholesterolemia (total and low-density lipoprotein cholesterol concentrations averaged 9.57 mmol/L (370 mg/dl) and 7.87 mmol/L (301 mg/dl)). After a 3-month strict diet, the children were given sitosterol pastils (2 gm three times a day) for 3 months, followed by a 7-month course of sitostanol (0.5 gm three times a day). Serum lipoprotein levels and serum concentrations of campesterol and sitosterol were determined in all nine children, and the fecal excretion of neutral and acidic sterols were determined in seven children at the end of each therapeutic regimen. Sitosterol reduced low-density lipoprotein cholesterol levels by 20% ($p < 0.01$); sitostanol reduced low-density lipoprotein cholesterol levels by 33% after 3 months and 29% after 7 months ($p < 0.01$ compared with diet; $p < 0.05$ compared with sitosterol). Although sitosterol did not alter serum concentrations of campesterol and sitosterol, a significant reduction did occur during sitostanol therapy (-47% and -51%, respectively; $p < 0.01$). Fecal excretion of neutral sterols increased from 6.7 mg/kg per day during the control period to 9.7 mg/kg per day during sitosterol administration ($p < 0.05$), and to 12.6 mg/kg per day during sitostanol administration ($p < 0.05$ compared with diet and sitosterol periods), indicating an increase in the inhibition of intestinal cholesterol absorption. All children completed the study and no obvious side effects occurred. The data indicate that sitostanol, even with a dose four-fold lower than that of sitosterol, was significantly more effective in reducing elevated levels of low-density lipoprotein cholesterol, and the reduction in serum lipid levels was of the same magnitude as that observed with systemic lipid-lowering drugs. These results suggest that sitostanol, a nonabsorbable plant sterol, could be the drug of choice for treating familial hypercholesterolemia in childhood.

Clin Chim Acta 1992 Jan 31;205(1-2):97-107

Effects of unsaturated and saturated dietary plant sterols on their serum contents.

Vanhanen HT, Miettinen TA

Second Department of Medicine, University of Helsinki, Finland.

Rapeseed oil fed to 24 hypercholesterolemic patients (50 g/day) reduced serum cholesterol (-8.5%) and cholestanol concentrations but increased those of campesterol and sitosterol. Continuation of rapeseed oil alone or with added sitosterol (625 mg/day) or sitostanol (630 mg/day) had no further effect on serum cholesterol. Rapeseed oil with sitosterol increased further its own proportion to cholesterol in serum but reduced that of campesterol while rapeseed oil with sitostanol reduced the proportions of both sitosterol and campesterol proportionately to the

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pretreatment values. The changes in the campesterol and sitosterol proportions were negatively and positively related to each other during the sitosterol and sitostanol additions, respectively. Thus, concentrations of unsaturated plant sterols in serum reflect their dietary intakes, saturated plant sterols are virtually not absorbed, plant sterols interfere with absorption of unsaturated structurally different plant sterols and cholestanol, and plant sterol-induced reduction of sterol absorption may be positively related to absorption efficiency of sterols.

Pediatrics 1992 Jan;89(1):138-42

Long-term treatment of severe familial hypercholesterolemia in children: effect of sitosterol and bezafibrate.

Becker M, Staab D, Von Bergman K

Department of Pediatrics, University of Bonn, Federal Republic of Germany.

Seven prepubertal children (age range 5.3 to 10.8 years) with severe heterozygous familial hypercholesterolemia (serum cholesterol concentration 416 +/- 85 mg/dL and low-density lipoprotein [LDL] cholesterol concentration 360 +/- 90 mg/dL) were first treated by dietary intervention, second by sitosterol (3 x 2 g/d), and third by bezafibrate (2 x 200 mg/d). Each treatment period lasted 3 months. Subsequently, a treatment combining half the dose of sitosterol and bezafibrate was administered for the following 24 months. Diet alone reduced total and LDL cholesterol values by 4.5% (not significant) and 6.6% (P less than .05), respectively. Sitosterol lowered total and LDL cholesterol values by 17% (P less than .05) when compared with diet alone. Compared with sitosterol, bezafibrate produced a more pronounced effect on total and LDL cholesterol values (-18% and -28%, P less than .05), and high-density lipoprotein cholesterol concentration increased significantly from 48 mg/dL to 55 mg/dL. Combined treatment with half the dose each of sitosterol and bezafibrate was as effective as the higher dose of bezafibrate, and reduction averaged almost 40% and 50% for total and LDL cholesterol values; this lipid-lowering effect persisted for the next 24 months. Laboratory safety parameters and physical examination revealed no obvious side effects. This study indicates that the combination of sitosterol (3 x 1 g/d) plus bezafibrate (1 x 200 mg/d) is an alternate, acceptable, safe, and effective therapeutic approach for treatment of severe hypercholesterolemia in children with high-risk familial hypercholesterolemia.

Metabolism 1991 Aug;40(8):842-8

Relationships of serum plant sterols (phytosterols) and cholesterol in 595 hypercholesterolemic subjects, and familial aggregation of phytosterols, cholesterol, and premature coronary heart disease in hyperphytosterolemic probands and their first-degree relatives.

Glueck CJ, Speirs J, Tracy T, Streicher P, Illig E, Vandegrift J
Jewish Hospital Cholesterol Center, Cincinnati, OH 45229.

To assess relationships of serum phytosterols (plant sterols [P]) to serum cholesterol (C), P were measured by gas-liquid chromatography (GLC) in 595 hypercholesterolemics (top C quintile in screening of 3,472 self-referred subjects). A second specific aim was to determine whether high serum P would track over time and whether they would predict familial aggregation of high C, high low-density lipoprotein cholesterol (LDLC), high apolipoprotein (apo) B, and increased premature coronary heart disease (CHD) in hyperphytosterolemic probands and their first-degree relatives. Mean +/- (SD) C was 260 +/- 56 mg/dL, campesterol (CAMP) was 2.10 +/- 1.6 micrograms/mL, stigmasterol (STIG) 1.71 +/- 1.67, sitosterol (SIT) 2.98 +/- 1.61, and total P 6.79 +/- 3.66 micrograms/mL. Serum C correlated with CAMP (r = .15, P less than or equal to .001), STIG (r = .10, P less than or equal to .02), SIT (r = .34, P less than or equal to .0001), and total P (r = .29, P less than or equal to .0001). High serum CAMP and STIG were associated with

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a personal or family history of CHD in subjects less than or equal to age 55 years (premature CHD). In 21 hyperphytosterolemic probands who initially had at least one P at or above the 95th percentile and a second P at or above the 75th percentile, P were remeasured 2 years later. Initial and 2-year follow-up CAMP, STIG, and SIT did not differ (P greater than .7). Initial and follow-up CAMP were correlated ($r = .47$, $P = .03$).

Eur J Clin Pharmacol 1991;40 Suppl 1:S59-63

Mechanisms of action of plant sterols on inhibition of cholesterol absorption. Comparison of sitosterol and sitostanol.

Heinemann T, Kullak-Ublick GA, Pietruck B, von Bergmann K
Department of Medicine, University of Bonn, Federal Republic of Germany.

The effects of two different plant sterols on intestinal cholesterol absorption were compared in normal volunteers by an intestinal perfusion study during a control period followed by high dose infusion of sitosterol or sitostanol (3.6 $\mu\text{mol}/\text{min}$), to which subjects were allocated in a randomized manner. Cholesterol absorption during the control period was similar in the two groups, averaging $0.88 \pm 0.48 \mu\text{mol}/\text{min}$ (32 \pm 11%) for group I (sitosterol) and $0.68 \pm 0.33 \mu\text{mol}/\text{min}$ (29 \pm 9%) for group II (sitostanol). The infusion of a high dose of sitosterol resulted in a significant reduction of cholesterol absorption to $0.47 \mu\text{mol}/\text{min}$ (16%). Following the same dose of sitostanol, cholesterol absorption diminished significantly to $0.15 \pm 0.11 \mu\text{mol}/\text{min}$ (5.1 \pm 2.9%). Overall cholesterol absorption declined during sitosterol infusion by almost 50%, whereas sitostanol infusion caused a reduction of cholesterol absorption by almost 85%. These findings of a more effective inhibition of cholesterol absorption by sitostanol might confirm the observation recorded by others that an increase in hydrophobicity of a plant sterol results in a higher affinity but lower capacity to mixed micells. This may cause an effective displacement of cholesterol from micellar binding and therefore diminished cholesterol absorption.

Am J Epidemiol 1990 Jan;131(1):20-31

Serum plant sterols and cholesterol precursors reflect cholesterol absorption and synthesis in volunteers of a randomly selected male population.

Miettinen TA, Tilvis RS, Kesaniemi YA
Second Department of Medicine, University of Helsinki, Finland.

To investigate the regulation of serum levels of cholesterol precursor sterols and plant sterols, these noncholesterol sterols, fatty acids, and various parameters of cholesterol metabolism were analyzed in 63 volunteers from a randomly selected Finnish male population sample of 100 subjects, aged 50 years, who had normal dietary habits. Serum levels of cholesterol precursors, desmosterol and lathosterol (in terms of micrograms/mg cholesterol), were negatively related to both the fractional and absolute absorption of dietary cholesterol and serum high density lipoprotein (HDL) cholesterol, and positively related to overall cholesterol synthesis and serum very low density lipoprotein (VLDL) cholesterol. Serum levels of the plant sterols, campesterol and sitosterol, exhibited positive correlations with the polyunsaturated/saturated fatty acid ratio of dietary fat, the linoleic acid contents of plasma and dietary lipids, the amount of dietary plant sterols (as indicated by fecal output), fractional and absolute absorption of dietary cholesterol, and HDL cholesterol, but were inversely related to the overall cholesterol synthesis and VLDL cholesterol. Stepwise multiple regression analysis revealed that the serum level of campesterol was associated with fractional cholesterol absorption, dietary plant sterols, and biliary cholesterol secretion, and that of sitosterol with dietary plant sterols, cholesterol synthesis, fractional cholesterol absorption, and biliary cholesterol secretion. Thus, the serum non-cholesterol sterols are significant indicators of cholesterol absorption and synthesis even under basal conditions and, since gas liquid chromatographic determination of these sterols is quite simple, their

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measurement may be valuable for monitoring cholesterol metabolism in large-scale epidemiologic studies.

Lipids 1989 Jan;24(1):9-12

Effect of sitosterol on the rate-limiting enzymes in cholesterol synthesis and degradation.

Boberg KM, Akerlund JE, Bjorkhem I

Institute of Clinical Biochemistry, University of Oslo, Norway.

Attempts were made to develop an animal model for phytosterolemia. Infusion of Intralipid containing 0.2% sitosterol in rats gave circulating levels of sitosterol of about 2.5 mmol/l, which is similar to or higher than those present in patients with untreated phytosterolemia. In addition, the infusions gave serum levels of cholesterol nearly twice those obtained in rats infused with Intralipid

alone or Intralipid containing 0.2% cholesterol. The hepatic HMG-CoA reductase activity was unaffected or slightly increased by the sitosterol infusions (not statistically significant). The cholesterol 7 alpha-hydroxylase activity was slightly depressed (ca. 30%). In the case of 7 alpha-hydroxylation of endogenous cholesterol, the depression reached statistical significance (p less than 0.05). The microsomal content of sitosterol in the sitosterol-infused rats was about 30% of that of microsomal cholesterol. The effect of sitosterol on 7 alpha-hydroxylation of cholesterol was investigated by incubations of acetone powder of rat liver microsomes with mixtures of cholesterol and sitosterol. Sitosterol mixed with cholesterol to a composition similar to that found in the above microsomal fraction had a depressing effect on 7 alpha-hydroxylation of cholesterol. This degree of depression was of the same magnitude as that found in the sitosterol infusion experiments. The possibility is discussed that the hypercholesterolemia obtained in the beta-sitosterol-infused rats is due to the inhibitory effect of sitosterol on the cholesterol 7 alpha-hydroxylase.

J Lipid Res 1988 Dec;29(12):1573-82

Inhibition of cholesterol absorption in rats by plant sterols.

Ikeda I, Tanaka K, Sugano M, Vahouny GV, Gallo LL

Department of Biochemistry, George Washington University, School of Medicine, Washington, DC 20037.

The extent and site(s) of inhibition of cholesterol absorption by plant sterols, sitosterol and fucosterol, were studied in rats. The intragastric administration of a single emulsified lipid meal containing 25 mg [³H]cholesterol and 25 mg of either sitosterol or fucosterol inhibited the lymphatic absorption of cholesterol by 57% and 41%, respectively, in 24 hr. Less than 2% of each plant sterol was absorbed in the 24-hr period. In contrast, neither plant sterol (50 microM) inhibited cholesterol absorption when co-administered with equimolar amounts of cholesterol in phospholipid-bile salt micelles nor was either absorbed from the micellar solution. A series of in vitro studies was conducted to identify the site(s) of plant sterol inhibition of cholesterol absorption and to account for the difference in inhibitory effectiveness of sitosterol and fucosterol. A comparison of the micellar solubility of each sterol alone and in equimolar binary mixtures (to 2.0 mM) revealed that the solubility of individual sterols decreased in the following order: cholesterol, fucosterol, sitosterol, and that in binary mixtures cholesterol solubility was decreased by sitosterol and, to a lesser extent, by fucosterol relative to its solubility alone. A comparison between micellar-solubilized cholesterol and either sitosterol or fucosterol for binding to isolated brush border membranes, intestinal mucin, or for esterification by either cholesterol esterase or acyl coenzyme A:cholesterol acyltransferase revealed moderate to no competition. The data suggest that plant sterols displace cholesterol from bile salt (taurocholate) micelles and that sitosterol is more effective than fucosterol in this capacity.

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Agents Actions Suppl 1988;26:117-22

Comparison of sitosterol and sitostanol on inhibition of intestinal cholesterol absorption.

Heinemann T, Pietruck B, Kullak-Ublick G, von Bergmann K
Department of Medicine, University of Bonn, F.R.G. No abstract available

J Lipid Res 1987 Oct;28(10):1144-55

Published erratum appears in *J Lipid Res* 1988 Jan;29(1):120

Thermodynamic and molecular determinants of sterol solubilities in bile salt micelles.

Armstrong MJ, Carey MC
Department of Medicine, Harvard Medical School, Boston, MA.

We examined, by reverse-phase high performance liquid chromatography (HPLC), the hydrophilic-hydrophobic balance of cholesterol and 12 non-cholesterol sterols and related this property to their equilibrium micellar solubilities in sodium taurocholate and sodium glycodeoxycholate solutions. Sterols investigated exhibited structural variations in the polar function (3 alpha-OH, 3 beta-OH, 3 beta-SH), nuclear double bonds (none, delta 5, or delta 7), side chain length (C27, C28, C29) and side chain double bonds (none, delta 22, or delta 24). In general, a sterol's hydrophilic-hydrophobic balance became progressively more hydrophobic (as exemplified by increasing HPLC retention values, k') with additions of side chain methyl (C28) and ethyl (C29) groups and with 3 beta-SH substitution of the 3-OH polar function. Side chain delta 22 and especially delta 24 double bonds rendered the sterols appreciably more hydrophilic, whereas a single nuclear double bond had little influence. Sterol solubilities (24 degrees C, 0.15 M Na+) were uniformly greater in 50 mM solutions of sodium glycodeoxycholate (range 0.15 to 2.5 mM) than in equimolar solutions of the more hydrophilic bile salt, sodium taurocholate (range 0.07 to 0.67 mM). For each bile salt system, a strong inverse correlation existed between micellar solubilities of sterols and their HPLC k' values, indicating that more hydrophilic sterols had greater micellar solubilities than the more hydrophobic ones. Based upon the aqueous monomeric solubilities of cholesterol (C27) and beta-sitosterol (C29) at 24 degrees C, we derived free energy changes associated with micellar binding and found that solubilization of both sterols was more energetically favored in glycodeoxycholate solutions. Although cholesterol exhibited a higher binding affinity than beta-sitosterol in glycodeoxycholate micelles, solubilization of beta-sitosterol in taurocholate micelles was more energetically favored than cholesterol by -0.6 kcal/mol. Based upon these results we offer a thermodynamic explanation for the greater micellar solubilities of more hydrophilic sterols and suggest that the high affinity, but low capacity, of a typical phytosterol for binding to trihydroxy bile salt micelles may provide a physical-chemical basis for its inhibition of intestinal cholesterol absorption.

Relationship between absorption of cholesterol and serum plant sterols.

Nutr Rev. 1987 Jun;45(6):174-5. Review. No abstract available. No authors.

Am J Clin Nutr 1986 Jan;43(1):92-7

Serum plant sterols and their relation to cholesterol absorption.

Tilvis RS, Miettinen TA

beta-Sitosterol and campesterol were measured in serum lipoproteins of 17 subjects from two families. The serum levels of the two phytosterols were closely correlated with each other ($r = 0.974$), less consistently with serum cholesterol ($r = 0.489$), and not at all with serum triglycerides. As compared to cholesterol, serum free and esterified phytosterols tended to be accumulated in

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HDL where the phytosterol/cholesterol ratios were almost 40% higher than in VLDL and LDL. The serum phytosterol concentrations, the phytosterol/cholesterol ratios, especially in VLDL and LDL, and the fractional absorption of cholesterol were higher in women than in men. The levels of the phytosterols in whole serum and in each lipoprotein were significantly correlated with the percentage absorption of dietary cholesterol but were independent of the amount of dietary cholesterol and plant sterols. Our findings suggest that, in general, serum levels of noncholesterol sterols are effectively determined by the absorption which in turn is proportionate to the fractional absorption of cholesterol.

Pharmacol Ther 1985;31(3):177-208

Effect of plant sterols on serum lipids and atherosclerosis.

Pollak OJ. No abstract available

Mayo Clin Proc 1984 Apr;59(4):251-7

Primary hypercholesterolemia: effect of treatment on serum lipids, lipoprotein fractions, cholesterol absorption, sterol balance, and platelet aggregation.

Briones ER, Steiger D, Palumbo PJ, Kottke BA

The nonabsorbable bile acid sequestrant resin, colestipol, was administered to 16 patients with primary hypercholesterolemia, and its effect on serum lipids, lipoprotein fractions, and circulating platelet aggregate ratio and platelet aggregation in response to adenosine diphosphate (ADP) was compared with that of sitosterol. Cholesterol absorption and sterol balance studies were done in four of the subjects during the following treatment periods: diet alone, colestipol, and sitosterol. Total serum cholesterol was significantly reduced by colestipol but only slightly decreased by sitosterol. Combination treatment with colestipol and sitosterol was associated with a smaller decrease in serum cholesterol than was demonstrated with colestipol alone. Serum triglycerides tended to increase during colestipol therapy (this increase was not clinically significant) but showed a minimal nonsignificant decrease with sitosterol treatment. Colestipol decreased cholesterol absorption, whereas sitosterol slightly increased it. Fecal sterol excretion was increased with colestipol treatment but was minimally affected by administration of sitosterol. Low-density lipoprotein and high-density lipoprotein cholesterol significantly decreased with colestipol treatment. The circulating platelet aggregate ratio was significantly lower in the group of patients with hypercholesterolemia who received colestipol initially than in control subjects, but platelet aggregation in response to ADP was not significantly different between these two groups. No significant change in platelet aggregation was noted during colestipol or sitosterol treatment despite a significant decrease in total serum cholesterol with colestipol therapy, a suggestion that the platelet and lipid abnormalities are not interrelated.

Atherosclerosis 1984 Dec;53(3):225-32

Effects of feeding cholesterol and mixed plant sterols on the fecal excretion of acidic steroids in rhesus monkeys.

Bhattacharyya AK, Eggen DA

The effects of feeding diets with high or low amounts of cholesterol and with low or high levels of mixed plant sterols (sitosterol: campesterol: stigmasterol, 60:35:5) on the daily fecal excretion of acidic steroids were studied in rhesus monkeys. During periods of low dietary plant sterol, total fecal acidic steroid excretion was 43% lower (P less than 0.01) during low dietary cholesterol than during high dietary cholesterol. During periods of high dietary plant sterols the fecal

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acidic steroid excretion was 113% higher (P less than 0.01) with low dietary cholesterol than with high dietary cholesterol. Addition of mixed plant sterols to the low-cholesterol diet produced nearly a 2-fold increase (P less than 0.005) whereas, such an addition to the high cholesterol diet produced a significant decrease by about 53% (P less than 0.025) in the total fecal acidic steroid excretion. The results suggest that the effect of cholesterol feeding on fecal acidic steroid excretion depends on the level of plant sterols in the diet. This interaction of the effects of cholesterol and plant sterols on the fecal acidic steroid excretion is probably related to the inhibitory effect of plant sterols on cholesterol absorption.

J Lipid Res 1984 Mar;25(3):236-45

Changes in biliary and fecal bile acids in mice after treatments with diosgenin and beta-sitosterol.

Uchida K, Takase H, Nomura Y, Takeda K, Takeuchi N, Ishikawa Y

Diosgenin and beta-sitosterol (1% in diet) were administered to CRJ:CD-1 male mice for 15 days, in order to examine the changes in bile acid metabolism. There were some differences between diosgenin and beta-sitosterol in their effects on diet intake, liver weight, and plasma cholesterol level. However, both phytosterols caused no statistically significant changes in body weight gain, decreased cholesterol absorption to about one-third that observed in control mice, decreased liver cholesterol level, increased fecal excretion of cholesterol, and decreased fecal excretion of bile acids. Most of the increase in fecal excretion of cholesterol occurred 2 days after the start of feeding of phytosterols and gradually declined thereafter, but the levels on day 15 were nevertheless higher than those in the control mice. The fecal excretion of bile acids decreased progressively after the treatment with phytosterols. The decrease of bile acid derived from chenodeoxycholic acid was more predominant than the decrease of those derived from cholic acid, resulting in an increase of the cholic acid/chenodeoxycholic acid ratio. The biliary cholesterol, phospholipid, and bile acid mole % ratios and the lithogenic index were not changed, but the percentages of cholic acid and its related bile acids (the cholic acid group) to the total bile acids increased and those of the chenodeoxycholic acid group decreased after the treatments. The pool size of bile acids decreased in the mice given diosgenin but not in those given beta-sitosterol. Distribution of bile acids between the gallbladder and intestine was not altered by either phytosterol.

Biochim Biophys Acta 1983 Aug 10;732(3):651-8

Some aspects of mechanism of inhibition of cholesterol absorption by beta-sitosterol.

Ikeda I, Sugano M

Mixed bile salt micelle solubilized either cholesterol or beta-sitosterol to a comparable extent. When added simultaneously, beta-sitosterol restricted the micellar solubility of cholesterol. beta-Sitosterol also reduced the cholesterol content in the aqueous (micellar) phase of the intestinal contents of rats, the extent of reduction being comparable with that observed in vitro. The intestinal uptake of cholesterol in vivo was equivalent to the micellar incorporation of cholesterol both in vitro and in vivo. beta-Sitosterol had no inhibitory effect on cholesterol absorption from the micellar solution in jejunal loops in situ, whereas the rate of beta-sitosterol uptake was only about one-fifth that of cholesterol. The intestinal uptake of beta-sitosterol intubated into the stomach of rats was about one-fifth that of cholesterol. The intestinal brush-border membrane discriminated these sterols. These results suggest that the restriction of the micellar solubility of cholesterol, rather than the inhibition of uptake from brush-border membrane, is the major determinant for the interference of beta-sitosterol with cholesterol absorption.

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Am J Clin Nutr 1983 May;37(5):805-9

Comparative lymphatic absorption of sitosterol, stigmasterol, and fucosterol and differential inhibition of cholesterol absorption.

Vahouny GV, Connor WE, Subramaniam S, Lin DS, Gallo LL

Studies have been conducted on the lymphatic absorption of sitosterol (24 alpha-ethyl cholesterol), stigmasterol (delta 22, 24 alpha-ethyl cholesterol), and fucosterol (24-ethylidene cholesterol) when administered intragastrically to rats. In addition, the effect of each sterol on absorption of endogenous cholesterol has been assessed by including tracer cholesterol in the administered test emulsion. Analysis of 24-h lymph collections by GLC-mass spectrometry demonstrated that all three sterols were poorly absorbed to the extent of only 3 to 4% of the administered dose of 50 mg. In contrast, cholesterol absorption under similar conditions was about 42% of the administered dose. Administration of either sitosterol or stigmasterol resulted in an equally effective inhibition of cholesterol absorption (54%). Under identical conditions fucosterol had no effect on absorption of luminal cholesterol. The data suggest that the mechanism(s) for intestinal discrimination of sterols for absorption may be independent of the mechanism for interference with efficient cholesterol uptake by the intestine.

Jpn J Pharmacol 1983 Feb;33(1):103-12

Effects of spinasterol and sitosterol on plasma and liver cholesterol levels and biliary and fecal sterol and bile acid excretions in mice.

Uchida K, Mizuno H, Hirota K, Takeda K, Takeuchi N, Ishikawa Y

Effects of spinasterol and sitosterol on plasma and liver cholesterol levels and biliary and fecal sterol and bile acid excretions were examined with male mice. Both phyosterols were added to the diet at a 1% concentration and fed to mice for 15 days. Spinasterol increased the fecal cholesterol excretion and decreased the plasma and liver cholesterol levels, the bile acid pool size and the fecal bile acid excretion, especially those derived from chenodeoxycholic acid. Fecal coprostanol excretion remained unchanged. These changes were similar to those produced by sitosterol. These data led to the conclusions 1) that spinasterol, as well as sitosterol, inhibits cholesterol absorption, resulting in decreases of the plasma and liver cholesterol levels and 2) that when cholesterol absorption is inhibited, the synthesis of bile acids, especially that of chenodeoxycholic acid, decreases, suggesting that the dietary cholesterol is preferentially metabolized to chenodeoxycholic acid in mice.

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J Nutr Sci Vitaminol (Tokyo) 1982 Apr;28(2):117-26

Effects of beta-sitosterol on the concentrations of serum and liver cholesterol and serum apolipoproteins in rats fed butter fat.

Sugano M, Ikeda I, Imaizumi K, Watanabe M, Andoh M

Male rats were fed on semipurified cholesterol-free diets containing butter fat with or without supplementary beta-sitosterol. The expected rise of serum cholesterol caused by butter fat, as compared with safflower oil, was not able to be demonstrated, and hence the hypocholesterolemic effect of beta-sitosterol as well. However, the plant sterol effectively lowered the liver cholesterol level. Similar responses were also observed in mice. The distribution of cholesterol in serum lipoproteins remained unchanged among different dietary regimens. Butter fat increased the concentration of serum apoA-I in relation to safflower oil. There was possibly a trend toward higher serum apoA-I with supplementation of beta-sitosterol in a butter-fat diet. The effect of the plant sterol on serum apoB was rather variable. The observation strongly suggests that alteration in cholesterol metabolism in these rodents may not satisfactorily be estimated by the serum cholesterol parameter alone when diets free of cholesterol are fed. The concentration of hepatic cholesterol and serum apolipoproteins seems a more apposite measure for this purpose.

Am J Clin Nutr 1982 Apr;35(4):697-700

Optimizing the effect of plant sterols on cholesterol absorption in man.

Mattson FH, Grundy SM, Crouse JR

During three experimental periods, nine adults were hospitalized on a metabolic ward and fed a meal containing 500 mg of cholesterol as a component of scrambled eggs. In addition, the meal contained: 1) no additive, 2) 1 g beta-sitosterol, or 3) 2 g beta-sitosteryl oleate. Stools for the succeeding 5 days were analyzed to determine the percentage of the cholesterol in the test meal that was absorbed. The addition of beta-sitosterol resulted in a 42% decrease in cholesterol absorption; the beta-sitosteryl oleate caused a 33% reduction. These results indicate that the judicious addition of beta-sitosterol or beta-sitosteryl oleate to meals containing cholesterol-rich foods will result in a significant decrease in cholesterol absorption, with a consequent decrease in plasma cholesterol.

Lancet 1981 May 23;1(8230):1157

Lowering plasma cholesterol with beta-sitosterol and diet.

Drexel H, Breier C, Lisch HJ, Sailer S No abstract available.

Lipids 1979 Mar;14(3):285-91

The content and composition of sterols and sterol esters in sunflower and poppy seed oils.

Johansson A

The composition and proportion of free sterols and sterol esters in crude sunflower and poppy seed oils were determined, using preparative thin layer chromatography followed by gas chromatography with cholesterol as an internal standard. Free sterols and sterol esters were also isolated in a liquid fraction obtained by low temperature crystallization (-80 C) of the oils and enriched with minor lipid classes. This enrichment procedure provided a liquid fraction suitable for studies of minor components in the oils. However, selectivity towards sterol esters was observed since sterols esterified to very long chain fatty acids (C20-C24) were preferentially retained in the precipitate. The proportion of free and esterified sterols were found to be 0.34% and 0.28%, respectively, in the sunflower oil, whereas the corresponding figures for poppy seed oil were 0.33% and 0.05%. Sunflower oil was characterized by a relatively high percentage of delta 7-sterols, preferentially obtained in the esterified fraction, and by very long chain saturated

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fatty acids of sterol esters. The sterols in poppy seed oil were composed almost entirely of campesterol, stigmasterol, sitosterol and delta 5-avenasterol, although their percentage distributions were remarkably different in the free and esterified fraction.

J Pharm Sci 1979 Feb;68(2):245-7

Antihypercholesterolemic studies with sterols: beta-sitosterol and stigmasterol.

Chandler RF, Hooper SN, Ismail HA

Stigmasterol, which differs from beta-sitosterol by unsaturation at C22, was tested for antihypercholesterolemic activity under an experimental protocol that gave the results expected with beta-sitosterol and cholestyramine. In terms of serum cholesterol, stigmasterol had a barely significant antihypercholesterolemic effect while exhibiting no obvious effect on the heart or liver. It was concluded that saturation of the side chain, at least at C22, is important in conferring antihypercholesterolemic activity on a sterol.

Scand J Gastroenterol 1978;13(5):573-6

Fecal beta-sitosterol in patients with diverticular disease of the colon and in vegetarians.

Miettinen TA, Tarpila S

Fecal sterol analysis showed that excretion of beta-sitosterol, a major component of poorly absorbable dietary vegetable sterols, is subnormal in patients with diverticular disease of the colon. Thus, the patients had evidently consumed a diet low in plant materials. The finding agrees with the current opinion that diverticular disease of the colon is associated with dietary fibre deficiency and suggests that fecal beta-sitosterol provides a rough measure of the vegetable intake. In vegetarians the beta-sitosterol excretion was actually high.

J Am Diet Assoc 1978 Jul;73(1):39-47

Sterol content of foods of plant origin.

Weihrauch JL, Gardner JM

Available data on phytosterols from the world's literature have been compiled and summarized. There still exists a paucity of data on the quantities of plant sterols in many foods. More extensive data are available on the relative sterol composition. Our compilation shows that plant oils are excellent sources of phytosterols. Nuts and seeds contain moderate levels, and fruits and vegetables generally contain the lowest concentrations of plant sterols. Analyses of the minor sterols, namely, the delta5- and delta7-phytosterols, have become available only recently.

J Nutr 1977 Nov;107(11):2011-9

A comparison of hypocholesterolemic activity of beta-sitosterol and beta-sitostanol in rats.

Sugano M, Morioka H, Ikeda I

The hypocholesterolemic activity of beta-sitosterol and its hydrogenated product, beta-sitostanol (dihydro-sitosterol or stigmastanol) has been compared in young male rats. When cholesterol was included in the diet, sitostanol consistently exhibited significantly greater hypocholesterolemic activity than sitosterol. There were no apparent differences in the effects of the sterol and the stanol on the concentration of liver cholesterol and triglyceride. Increases in plasma triglyceride due to feeding sitosterol were not observed with sitostanol. Incorporation of dietary sitostanol into plasma, liver and other tissues was always negligible, and thus this stanol was almost completely recovered in feces, while there was considerable deposition of sitosterol (mean fecal recovery being 85% to 92%). The increase in fecal output of dietary cholesterol was significantly greater with the stanol than with sterol. There was no demonstrable negative effect on growth and weight

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of major visceral tissues in rats fed the sterol as well as the stanol. These observations together with those reported previously indicate that hydrogenation of phytosterols is a novel approach to enhance their hypocholesterolemic activities without influencing the relative safety of the initial sterols.

J Nutr 1977 Jul;107(7):1139-46

Effect of plant sterol esters on the absorption of dietary cholesterol.

Mattson FH, Volpenhein RA, Erickson BA No abstract available.