Advances In Therapy® | *Volume 20 No. 1*
January/February 2003

Advances In Natural Therapy™

Effects of Soy and Other Natural Products on LDL:HDL Ratio and Other Lipid Parameters: A Literature Review

Kjeld Hermansen, MD, DMSc
Department of Endocrinology and Metabolism
Aarhus University Hospital
Aarhus, Denmark

Bo Dinesen, MSc
Lars H. Hoie, MD
Nutri Pharma ASA
Copenhagen, Denmark

Eve Morgenstern, PhD
Joerg Gruenwald, PhD
Nutri Pharma GmbH
Berlin, Germany

ABSTRACT

Abnormal lipid levels contribute significantly to the risk of coronary heart disease, a major cardiovascular disease and a serious health problem. Various dietary and pharmacologic treatments have been devised to reduce elevated blood cholesterol levels. Soy protein, soluble fiber, and plant sterol/ester–containing margarines are promising new food-component candidates that may help to realize this goal. Of particular interest in this context is the LDL:HDL ratio, a strong predictor of cardiac events. This report is a review of more than 50 recent trials to determine how such dietary components and garlic affect the LDL:HDL ratio and other lipid parameters. Consumption of new soy products containing high, fixed levels of isoflavones, cotyledon soy fiber, and soy phospholipids (Abacor® and Abalon®) significantly reduced the LDL:HDL ratio by up to 27%. Soluble dietary fibers such as psyllium and beta glucan from oat bran had a variable effect on LDL-cholesterol levels in the studies analyzed. Plant sterol esters, when consumed in margarines, lowered the LDL:HDL ratio by up to 22%. On average, Abacor and Abalon reduced the LDL:HDL ratio by 20%, LDL cholesterol by 15%, total cholesterol by 10%, and triglycerides by 6%, and increased HDL cholesterol by 5%. The new soy-based supplements may therefore play a valuable role in reducing cardiovascular risk.

Keywords: hypercholesterolemia; soy protein; beta glucan; phytosterol; dietary fiber; lipid lowering; cardiovascular disease

0678

Address reprint requests to
NutriPharma ASA
Konprinsesesse Märthas pl. 1, Vika
0116 Oslo
Norway

INTRODUCTION

Abnormal lipid levels contribute significantly to the risk of coronary heart disease (CHD), and hypercholesterolemia is a recognized major risk factor. Large randomized trials have strongly suggested that a lowering of low-density lipoprotein (LDL)–cholesterol levels reduces the risk of CHD and myocardial infarction. Epidemiologic data have shown that low levels of high-density lipoprotein (HDL) cholesterol and high levels of triglycerides increase CHD risk. The robust inverse relationship between HDL cholesterol and CHD risk holds true for both sexes. In the Helsinki Heart Study, a high LDL:HDL cholesterol ratio (>5) was the strongest predictor of cardiac events.[1] An analysis of baseline serum lipid levels from three large prospective studies in young men demonstrated a continuous, graded relationship of serum cholesterol level to long-term risk of CHD, death from cardiovascular disease, and all-cause mortality.[2]

CHD prevention generally includes lifestyle modification and control of risk factors such as smoking, hypertension, and diabetes. Because many individuals are unable to achieve desirable LDL- and HDL-cholesterol levels with diet and lifestyle changes alone, however, recent decades have seen the introduction of various dietary supplements to pharmacologic therapies. Supplements with mild cholesterol-reducing properties can improve the outlook for patients whose LDL-cholesterol concentrations do not warrant treatment with the usual cholesterol-lowering drugs. The efficacy and safety of these different supplements have been documented in numerous studies.

Decreasing blood cholesterol has a powerful effect: a 10% reduction may lower the incidence of CHD by approximately 30%.[3] The US Food and Drug Administration (FDA) has acknowledged that consumption of soy protein and soluble fibers, eg, beta glucan from oat products and psyllium as well as plant sterol and stanol esters, significantly reduces blood cholesterol levels and the concomitant risk of CHD.[4-7]

This review of mainly post-1995 literature aims to evaluate how effectively blood lipids are affected by the use of different natural compounds as food supplements or food ingredients.

MATERIALS AND METHODS

Studies of the effect of soy products, dietary fibers from oat and psyllium, and phytosterols and phytostanol esters were identified by a computerized literature search in the medical databases Medline and Health Star. The review included predominantly studies published from 1995, but recent meta-analyses were also incorporated, as many investigations of oats and psyllium were carried out before 1995. Studies and meta-analyses of garlic preparations were also considered to compare the effects of a herbal product with those of the natural products discussed. The included studies had the following characteristics: (1) controlled, randomized, parallel, or crossover design; (2) discussion of lipid changes in the supplement and control groups; (3) adult populations; and (4) single preparations from a single natural source.

Results are quoted with and without subtraction of control values to capture potential maximal effects. Net changes in total, LDL, and HDL cholesterol, triglycerides, and the LDL:HDL ratio were calculated by subtraction of lipid changes after the control diet from lipid changes after use of the corresponding natural product.

Abacor®* is a product based on isolated soy protein (ISP) with a standardized high level of the isoflavones containing soy fiber and soy lecithin. ISPs are manufactured from defatted soy flakes by separation of the protein from the carbohydrates of the soybean. The ISP products discussed in this review contained more than 90% protein, with small amounts of flavoring and coloring agents.[8] The soy amino-acid profile is similar to that of milk and eggs and meets human nutritional requirements.[9]

RESULTS

Effect of Soy Products on Blood Lipids

Animal, epidemiologic, and human studies have demonstrated that a diet high in soy protein and low in animal protein reduces levels of serum total and LDL cholesterol as well as triglycerides. In a meta-analysis of 38 controlled clinical trials,[10] daily intake of 47 g of soy protein decreased serum levels of total cholesterol by 0.6 mM (9%), LDL by 0.56 mM (13%), and triglycerides by 0.15 mM (11%). Soy consumption was associated with a nonsignificant 2% increase in HDL cholesterol. In 1999, the FDA approved labeling claims that dietary intake of 25 g of soy protein per day may reduce the risk of CHD.[7]

Studies with New Soy Products

Four studies[11-14] have investigated Abacor and Abalon®,* two new ISP products with standardized high levels of isoflavones, soy cotyledon fibers, and soy lecithin (Table 1).

A randomized, placebo-controlled, double-blind, parallel-group trial[11] tested 31 men and 21 women with moderate hypercholesterolemia (total cholesterol 7.0–9.9 mM). After randomization, the active group consumed Abacor as a beverage for 6 weeks; the control group consumed a placebo based on casein and cellulose with the same protein and fiber content. Abacor significantly reduced total cholesterol by 9%, compared with 5% in the placebo group ($P<.001$). The total cholesterol-lowering effect was significantly larger with Abacor than with placebo ($P<.05$), as was the effect on LDL reduction (13% vs 8%). HDL cholesterol rose and triglycerides decreased nonsignificantly. Of 60 initial participants, 6 from the Abacor group and 2 from the placebo group withdrew because of gastrointestinal complaints.[11]

Abacor was administered in a low-fat yogurt formulation to 69 moderately hypercholesterolemic patients, and 74 controls consumed unaltered low-fat yogurt for 8 weeks after an 8-week run-in during which participants ate a cholesterol-lowering diet.[12] Abacor decreased LDL cholesterol by a mean of 8% from baseline; no significant change occurred with placebo. At 8 weeks, the respective decreases had reached 12% and 5%, with simultaneous reductions of 10% and 5% in total cholesterol, corresponding to a mean 5% net change. LDL cholesterol dropped by 8% (net). The LDL:HDL ratio fell 7% with Abacor but rose 3% with placebo. HDL and triglyceride concentrations were not significantly changed. The lipid-lowering effects began after the first week of treatment.

*Registered trademark of NutriPharma ASA, Oslo, Norway.

Table 1. Effects of Abacor and Abalon on Blood Lipids

Preparation	Dose/d	Lipid Parameter, mM: Total Cholesterol Initial	End	% Change	Triglycerides Initial	End	% Change	LDL Cholesterol Initial	End	% Change	HDL Cholesterol Initial	End	% Change	LDL: HDL Ratio Treatment Initial	End	% Change	Placebo Initial	End	% Change	Study Duration, wk	Time to Maximum Effect, wk	No. of Participants
Abacor[11]*	52 g soy protein, 192 mg isoflavone +15.5 g SCF	7.5 ± 0.57	6.86† NR	−9†	0.76 ± 0.78	1.63† NR	−7*	5.13 ± 0.48	4.45† NR	−13†	1.58 ± 0.44	1.67† NR	+6†	3.25†	2.66†	−18†	(casein/fiber control)‡ 3.30†	2.89†	−12†	6	5	Treatment, 24 Control, 28
Abacor[12]*	41 g soy protein, 152 mg isoflavones +9 g SCF combined with yogurt	7.53 ± 0.79	6.81 ± 0.65	−10†	1.68 ± 0.80	1.64 ± 1.01	−6†	5.11 ± 0.69	4.50 ± 0.63	−12†	1.67 ± 0.53	1.57 ± 0.42	−6†	3.29 ± 0.91	3.06 ± 0.89	−7†	(low-fat yogurt)‡ 3.14	3.22	+3†	8	8	Treatment, 69 Control, 74
Abacor[13§]	AHA diet+ 30 g soy protein, 115 mg isoflavones +10 g SCF	6.86 ± 0.67	6.00 ± 0.55	−13†	1.28 ± 0.38	1.13 ± 0.45	−13†	4.81 ± 0.54	3.94 ± 0.45	−18†	1.48 ± 0.42	1.55 ± 0.45	+5†	3.25†	2.52†	−22†	(casein/fiber control)‡ 3.87†	3.26†	−16†	16	16	Treatment, 34 Control, 36
	50 g soy protein, 192 mg isoflavones +16.6 g SCF	6.52 ± 0.63	5.61 ± 0.71	−14†	1.33 ± 0.70	1.13 ± 0.62	−15†	4.58 ± 0.50	3.63 ± 0.53	−21†	1.35 ± 0.33	1.47 ± 0.36	+9†	3.39†	2.47†	−27†	(casein/fiber control)‡ 3.88‡	3.14†	−19†	16	16	Treatment, 31 Control, 29
Abalon[14*]	50 g ISP (total isoflavones >165 mg) + 20 g SCF control, 50 g casein + 20 g cellulose	5.68 ± 0.84	5.11 NR	−10‖	1.70 ± 1.17	1.63 NR	−5‖	3.63 ± 0.78	3.01 NR	−17‖	1.31 ± 0.22	1.38 NR	+5‖	2.77‖	2.18‖	−22‖	2.95	2.52	−15†	6 per treatment (crossover)	NR	20

SCF=soluble cotyledon fiber; NR=not reported; AHA=American Heart Association.
*Initial values from baseline after randomization.
†Calculated from study report data.
‡Calculated from control group data.
§Initial values after run-in period.
‖Calculated from cited published data.

The long-term dose-response effect of daily Abacor was studied in a parallel-group trial[13] of 159 mildly hypercholesterolemic men and postmenopausal women (mean age, 53 years) with LDL-cholesterol concentrations of 4 mM or more who followed a lipid-lowering diet (National Cholesterol Education Program [NCEP] or American Heart Association step 1) for 4 to 24 weeks before intervention. Participants were randomly assigned to two treatment and two control groups for 16 weeks. Treatment groups received either 31 or 52 g of soy protein with fixed levels of isoflavones and an additional 10 or 16.6 g of soy cotyledon fiber as ready-to-mix beverages. Control groups consumed 30 or 50 g of casein and 10 or 16.6 g of cellulose. Decreases of 13% in total cholesterol and 18% in LDL cholesterol occurred with 31 g of Abacor; corresponding decreases with placebo were 8% and 11%. In the 52-g Abacor group, total cholesterol dropped by 14% (placebo, 11%) and LDL cholesterol by 21% (placebo, 16%). The net changes for the 52-g group receiving ISPs were not significant. HDL cholesterol increased in all groups by 4% to 9%. Nineteen participants withdrew from the study, most because of compliance problems or gastrointestinal complaints. There were more withdrawals in the casein than in the soy groups.

A randomized, double-blind crossover trial of 20 outpatients investigated the effect of a product with soy protein, isoflavones, and cotyledon fiber (Abalon) on serum lipid levels in patients with type 2 diabetes.[14] Participants received supplementation with 50 g of soy protein daily or placebo for 6 weeks separated by a 3-week washout. Dietary intake was recorded and validated by a dietitian. Diets were isocaloric and had the same macronutrient composition for each patient. Maximum changes were observed, and the LDL:HDL ratio dropped by 22% (placebo, 15%). The net changes between Abalon and placebo revealed significant decreases of 10% in LDL, 12% in the LDL:HDL ratio, and 22% in triglycerides; the 8% decrease in total cholesterol did not reach statistical significance ($P<.08$).

Other Studies With ISP

The effects of soy preparations on blood lipids were studied in nine trials[15-23] (Table 2). The amount of soy protein needed to reduce serum lipids was tested in 81 moderately hypercholesterolemic men randomly assigned to one of five treatment groups after 3 weeks of the NCEP step 1 diet.[15] For 6 weeks each patient received 50 g of protein per day consisting of ISP with or without casein in the following amounts: 50:0, 40:10, 30:20, 20:30, or 0:50 (control group). Non–HDL-cholesterol percent concentrations decreased significantly with 20 (3%), 30 (3%), and 50 (4%) g of ISP, but not with 40 g. At 3 weeks, non-HDL cholesterol had fallen by a significant 5% in the 40-g group and by 6% in the 50-g group. The LDL:HDL ratio was reduced by 6%.

Sixty-six postmenopausal women with mild hypercholesterolemia were randomly assigned to an NCEP step 1 diet plus one of the following regimens: casein and nonfat dry milk (control), soy protein containing 56 mg of isoflavones, or soy protein containing 90 mg of isoflavones per day.[16] The daily protein supplement was 40 g, and the study lasted 24 weeks. All patients ate a standard diet for 2 weeks before treatment. Non-LDL cholesterol decreased more in the two groups consuming soy (8% with 56 mg, 9% with 90 mg) than in the control group (2%); HDL cholesterol increased in both soy groups but dropped by 4% in the control group. Total plasma triglyceride concentrations did not change significantly. The significantly greater LDL-receptor mRNA concentration noted at 24 weeks in both soy groups compared with the control group indicated that soy protein components may regulate lipid profiles through alterations in LDL receptor quantity or activity.

Table 2. Effect of Soy Preparations on Blood Lipids

Dose/d	Lipid Parameter, mM: Total Cholesterol Initial	End	% Change	Triglycerides Initial	End	% Change	LDL Cholesterol Initial	End	% Change	HDL Cholesterol Initial	End	% Change	LDL:HDL Ratio: Treatment Initial	End	% Change	Placebo Initial	End	% Change	Study Duration, wk	Time to Maximum Effect, wk	No. of Participants
NCEP step 1 diet + 50 g ISP[15]*	6.28 ±0.18	6.07 ±0.19	−3†	2.18 ±1.28	2.54 ±0.40	+17‡	5.15‡ ±0.19	4.92‡ ±0.18	−4‡	1.13 ±0.05	1.15 ±0.06	+2‡	4.56†‖	4.28†‖	−6†	4.53†‖	4.72†	+4†	6	3	Treatment,15 Control, 16
NCEP step 1 + 40 mg ISP with 90 mg aglycone isoflavones[16]*	6.47 ±0.88	6.13 ±0.91	−5†	1.74 ±0.75	1.74 ±0.96	0	5.09‡ ±1.03	4.71‡ ±1.09	−7†	1.38 ±0.32	1.42 ±0.31	+3†	3.69†	3.32‡	−10†	(control, casein/ nonfat dry milk) 3.52†	3.60‡	+2‡	24	18	Treatment, 21 Control, 22
As above but with 56 mg aglycone isoflavones	6.57 ±0.85	6.18 ±0.91	−6†	1.89 ±1.02	1.73 ±0.99	−8†	5.22‡ ±0.91	4.76‡ ±0.93	−9‡	1.34 ±0.27	1.42 ±0.31	+6†	3.89‡	3.35†	−14‡	(control, casein/ nonfat dry milk)			24	18	23
25 g ISP containing 62 mg isoflavones[17]*	6.28 ±0.67	6.03 ±0.52	−4†	1.73 ±0.67	1.72 ±0.75	−1†	4.29 ±0.65	4.03 ±0.44	−6†	1.19 ±0.23	1.22 ±0.28	+3†	3.61†	3.30†	−9†	3.68†	3.75†	+2†	9	NR	Treatment, 30 Control, 31
20 g ISP containing 34 mg isoflavones once daily[18]§	5.38 ±1.05	5.14 ±0.07‖	−4†	1.48 ±0.76	1.45 ±0.15‖	−2†	3.28 ±1.00	3.09 ±0.06‖	−6†	1.42 ±0.40	1.35 ±0.022‖	−5†	2.31†	2.29†	−1†	2.31†	2.35†	+2†	6	NR	51
As above, but with 2 doses/d	5.38 ±1.05	5.06 ±0.07‖	−6†	1.48 ±0.76	1.59 ±0.14‖	+7†	3.28 ±1.0	3.02 ±0.06‖	−8†	1.42 ±0.40	1.36 ±0.02‖	−5†	23.1†	2.24†	−3†						
≥75% of total protein content of NCEP diet	4.40 ±0.60	4.01 ±0.96	−9†	1.01 ±0.36	1.11 ±0.47	+10†	2.87 ±0.49	2.53 ±0.65	−12†	1.06 ±0.26	0.98 ±0.31	−8†	2.80 ±0.80	2.70 ±0.80	−4†	(control, meat) 2.90	2.90	0†	5	NR	13 normochol-esterolemic
50 g ISP[19]*	6.78 ±0.70	6.39 ±0.98	−6†	2.37 ±1.34	3.00 ±2.28	+27‡	4.68 ±0.64	4.09 ±1.09	−13‡	1.01 ±0.29	0.96 ±0.26	−5‡	5.00 ±1.60	4.50 ±1.30	−10†	(control, meat) 5.00	5.2	+4‡		NR	13 hypercho-lesterolemic
75–100 g soy powder with 128.7 mg isoflavone[20]¶	3.64 ±0.03‖	3.63 ±0.06‖	−0.3†	0.67 ±0.02‖	0.69 ±0.04‖	+3†	2.15 ±0.03‖	2.15 ±0.05‖	−1†	1.18 ±0.01‖	1.20 ±0.03‖	+2†	1.89 ±0.03‖	1.83 ±0.07‖	−3†	1.89 0.03‖	1.98 0.06‖	+5†	3 menstrual cycles	NR	13
85 g ISP with 65 mg isoflavones[21]*	5.55 ±0.68	4.99 ±0.07‖	−10†	1.46 ±1.29	1.22 ±0.08	−16‡	3.53 ±0.81	3.05 ±0.05	−14‡	1.35 ±0.43	1.38 ±0.02	+2†	2.90 ±1.40	2.49 ±0.06‖	−14†	2.9 ±1.40	2.72 ±0.05‖	−6†	13	NR	17
85 g ISP with 132 mg isoflavones	5.55 ±0.68	4.93 ±0.06‖	−11†	1.46 ±1.29	1.22 ±0.08‖	−16†	3.53 ±0.81	3.01 ±0.05‖	−15‡	1.35 ±0.43	1.36 ±0.02‖	+1†	2.90 ±1.40	2.51 ±0.05‖	−13†				13	NR	18
290 g tofu[22]§	5.79 ±0.97	5.42 ±1.02	−5†	1.96 ±1.33	1.62 ±0.99	−17†	3.68 ±0.86	3.48 ±0.92	−6†	1.25 ±0.35	1.24 ±0.27	−1†	2.94†	2.91†	−4†	2.94†	2.70†	−8† (control, lean meat 1550 g/d)	4 each diet	NR	42
31 g soy protein from soybean products[23]§	6.86 ±0.99	6.98 ±1.23	+2†	1.75 ±0.64	1.94 ±0.83	+11†	4.45 ±0.95	4.26 ±1.04	−4†	1.31 ±0.32	1.40 ±0.28	+7†	3.40‡	3.04†	−11†	3.40†	3.35‡	−1† (control, milk)	4 each diet	NR	34

NCEP=National Cholesterol Education Program; NR=not reported.
*Initial values after run-in period.
†Calculated from cited published data.
‡Non-HDL cholesterol or non-HDL:HDL ratio.
§Initial values from baseline.
‖Standard error.
¶Values during the midluteal phase are shown.

Table 3: Effect of Psyllium on Blood Lipids

Dose/d	Lipid Parameter, mM: Total Cholesterol Initial	Total Cholesterol End	Total Cholesterol % Change	Triglycerides Initial	Triglycerides End	Triglycerides % Change	LDL Cholesterol Initial	LDL Cholesterol End	LDL Cholesterol % Change	HDL Cholesterol Initial	HDL Cholesterol End	HDL Cholesterol % Change	LDL:HDL Ratio: Treatment Initial	Treatment End	Treatment % Change	Placebo Initial	Placebo End	Placebo % Change	Study Duration, wk	Time to Maximum Effect, wk	No. of Participants
10.2 g psyllium, NCEP step 1 diet (values from study end)[29*†]	6.19 ±0.10	6.14 ±0.12	−1‡	1.51 ±0.10	1.51 ±0.13	0	4.25 ±0.09	4.19 ±0.10	−2‡	1.25 ±0.05	1.29 ±0.04	+3‡	3.40‡	3.32‡	−5‡	NCEP step 1 diet alone 3.33‡	3.05‡	−8‡	24	4	Treatment, 42 Control, 58
10.2 g psyllium, NCEP step 1 diet (after 4 wk)[29*†]	6.19 ±0.10	5.98 ±0.11	−3‡	1.51 ±0.10	1.45 ±0.11	−4‡	4.25 ±0.09	4.06 ±0.09	−4‡	1.25 ±0.05	1.24 ±0.05	−1‡	3.40‡	3.27‡	−4‡	NCEP step 1 diet alone 3.33‡	3.39‡	+2‡	24	4	Treatment, 42 Control, 58
10.2 g psyllium, AHA step 1 diet[30§§]	5.93 ±0.04	5.08 ±0.05	−2	1.42 ±0.05	1.43 ±0.05	+3	3.99 ±0.03	3.86 ±0.04	−3	1.29 ±0.02	1.29 ±0.02	0	3.09‡	2.99‡	−3‡	Cellulose 3.34‡	3.42‡	+2‡	26	NR	Treatment, 197 Control, 51
7 g psyllium, standard CL diet[31*]	6.87	6.44	−6 ±0.07	NR	NR	NR	4.93	4.48	−9 ±0.05	NR	NR	NR	NR	NR	−11	NR		−8	12	NR	70
10.5 g psyllium, standard CL diet[31*]	6.93	6.49	−6 ±0.07	NR	NR	NR	4.99	4.49	−10 ±0.06	NR	NR	NR	NR	NR	−12	NR		−8	12	NR	64 Control, 62
15 g psyllium[32*]	5.43 ±0.88	5.04 ±1.09	−7‡ ±0.90	1.78 ±0.60	1.55	−13‡	3.65 ±1.29	3.05 ±0.88	−16‡	0.88 ±0.59	1.32 ±0.75	+50‡	4.15‡	2.31‡	−44‡	Inert bulk fiber from cellulose 4.40‡	4.00‡	−9‡	6	6	63 with type 2 diabetes Control, 60
1.7 g soluble fiber from psyllium[33*]	5.53 ±0.49	4.99 ±0.67	−10‡	1.74 ±0.76	1.74 ±0.82	0	3.78 ±0.41	3.13 ±0.52	−17	0.96 ±0.21	1.06 ±0.23	+9	4.20	3.00	−29	(control, wheat bran) 3.00	2.40	−20	8	NR	Treatment, 20 Control, 24
	6.98 ±0.47	5.69 ±0.08	−18†	2.40 ±1.55	2.39 ±1.51	0 0†	5.07 ±0.75	3.65 ±0.78	−28†	0.83 ±0.18	0.93 ±0.18	+12†	6.50	4.00	−38†	4.30	3.60	16			

NR=not reported; CL=cholesterol lowering.
*Inital values after run-in period.
†Standard error of the mean.
‡Calculated from published data.
§Initial values average taken at weeks −2, −1, 0.

In a randomized trial,[17] 156 healthy, mildly hypercholesterolemic men and women consumed an NCEP step 1 diet for 1 month followed by a similar diet supplemented with 25 g of casein daily for another month before being assigned to groups consuming 25 g of ISP, 62, 37, 27, or 3 mg of isoflavones, or 25 g of casein as control. Compared with casein, ISP with 62 mg of isoflavones lowered total and LDL cholesterol; an increase in the amount of isoflavones affected these lipid fractions in a dose-dependent manner. Plasma concentrations of HDL cholesterol and triglycerides were unaffected. Patients whose LDL-cholesterol levels exceeded 4.24 mM experienced a more pronounced effect with the 62-mg isoflavone dose than with any of the other doses; their total cholesterol dropped by 9%, LDL cholesterol by 10%. Ethanol-extracted soy protein with 3 mg of isoflavones did not reduce circulating levels of total or LDL cholesterol.

A double-blind, crossover trial randomly assigned 51 perimenopausal women with mild hypercholesterolemia to three daily isocaloric dietary supplements: 20 g of complex carbohydrates (control diet), 20 g of soy protein with 34 mg of isoflavones in a single dose, or the same diet supplement divided into two doses.[18] Each intervention period lasted 6 weeks. A significant 6% decrease in total cholesterol was observed in both soy diets compared with the carbohydrate control; LDL cholesterol also fell by 8%. The triglyceride level decreased, and the HDL-cholesterol level did not change, whereas the LDL:HDL ratio fell by 3% (20 g of ISP and 34 mg of isoflavones once daily) or by 5% with the split-dose regimen.

The ability of soy protein to enhance the hypocholesterolemic effect of the NCEP step 1 diet was also demonstrated in a randomized, two-part, crossover study[19] with 13 normocholesterolemic and 13 moderately hypercholesterolemic men. For 5 weeks, the treatment groups followed the NCEP diet in which soy protein comprised 75% or more of the total protein content; the placebo group received animal protein. On average, the study population consumed about 50 g of soy protein daily. After the NCEP diet, participants followed their usual diet for 10 to 15 weeks and were then crossed over to the alternate diet for another 5 weeks. Consumption of soy protein for 5 weeks produced a significant difference in the decrease of serum LDL-cholesterol concentrations between normocholesterolemic and hypercholesterolemic men on the one hand and controls on the other hand. The LDL:HDL ratio was 11% lower with a soy diet than with a control diet. Total cholesterol did not change significantly.

Isoflavones significantly improved the lipid profile across the menstrual cycle in a crossover trial[20] in 13 normocholesterolemic premenopausal women who consumed their usual diet and each of the three ISPs providing 10 (control), 65, and 129 mg of isoflavones daily. The daily amount of soy powder consumed as a beverage was 75 to 100 g, depending on body weight. Compared with the control diet, the high-isoflavone diet (129 mg) lowered LDL cholesterol by 8% in the midfollicular phase and by 10% in the periovulatory phase. The LDL:HDL ratio decreased from 2% to 8% in the early follicular phase and to 14% in the periovulatory phase. Isoflavone consumption did not significantly change total or HDL cholesterol or triglycerides.

In another randomized crossover trial,[21] 18 postmenopausal women received 85 g of ISP with an average of 7 (control), 65, or 132 mg of isoflavones daily for 93 days. When consumed as a constituent of soy protein, isoflavones lower LDL-cholesterol levels in normocholesterolemic or mildly hypercholesterolemic women. Compared with the control diet, 132 mg of isoflavones decreased serum LDL cholesterol by 7%. The difference between the high and low doses was not significant (P=.07); total and HDL cholesterol and triglycerides were not significantly affected.

Two crossover studies evaluated the efficacy of tofu[22] and a soybean product[23] instead of ISP preparations. Compared with a control diet with cow's milk, a diet with 31 g of protein from a soybean product produced a significant increase in HDL and a significant decrease in the LDL:HDL ratio after 4 weeks.[23] A 290-g tofu diet significantly reduced not only plasma total cholesterol but also the HDL concentration, compared with a 150-g lean meat diet.[22] Triglycerides decreased from baseline with both diets. Results of these two studies were not included in the final calculation.

Effect of Soluble Fibers on Blood Lipids

Diets high in complex carbohydrates including soluble fibers (pectins, gums, mucilages, and some hemicelluloses) reduce serum lipids in individuals with hypercholesterolemia. The mechanism remains unclear, but soluble fibers may bind bile acids or cholesterol during the intraluminal formation of micelles.[24] In patients undergoing resection for colonic cancer, oral intake of *Psyllium ovata* seeds stimulated the colonic flora to increase production of butyrate (and acetate) from this fiber and raised fecal concentrations of butyrate by 42%.[25] The major effect of beta glucan is related to increased bile excretion of cholesterol. A delay in the micellar lipid solubilization process and a consequent reduction in the secretion of chylomicrons into the circulation may also be operative.[26]

Psyllium

The term *psyllium* is used interchangeably to denote the seed husk, the seed, and the entire plant.[27] In 1998 the FDA included psyllium in its guidelines on health claims of foods containing soluble fibers, noting that in conjunction with a diet low in saturated fat and cholesterol, these foods may reduce the risk of cardiovascular disease. For these benefits to be achieved, 7 g of soluble psyllium fiber must be consumed daily.[5] Table 3 shows results of studies with psyllium.

In a meta-analysis[28] of eight controlled clinical trials involving patients with mild to moderate hypercholesterolemia, 384 patients received 10.2 g of psyllium per day, and 272 received cellulose as placebo. All studies evaluated the lipid-lowering effect of psyllium (7 to 10.2 g of soluble fiber) as a supplement to a low-fat diet (AHA step 1) for 8 or more weeks after a low-fat diet pretest period lasting at least 8 weeks. Psyllium consumption lowered serum total cholesterol by 4% and LDL cholesterol by 7%. Analyses by baseline triglyceride levels, sex, age, dose regimen, and formulation showed no between-subgroup differences when data were pooled across the studies. Psyllium intake was well tolerated and not associated with serious adverse effects.

The long-term effect of psyllium was studied in a randomized, double-blind, placebo-controlled trial in 286 patients with mild hypercholesterolemia.[29] After a low-fat NCEP step 1 diet for 8 weeks, patients were assigned to one of four treatment groups, consuming 0 (control), 3.4, 6.8, or 10.2 g of psyllium per day for 24 weeks. Serum LDL cholesterol rose by 3% in the control group and remained below baseline (5% lower than in controls) in the group consuming 10.2 g of psyllium; this effect, although modest, was significantly different from baseline and led to the conclusion that psyllium could have long-term value in controlling LDL cholesterol. No significant influence was seen on HDL-cholesterol and triglyceride levels. Strangely, a more pronounced reduction in the LDL:HDL ratio occurred in the control group than in the high-dose psyllium group.

In a multicenter study,[30] 284 patients with mild hypercholesterolemia were randomly assigned to consume either 10.2 g of psyllium or cellulose daily for 26 weeks after following the AHA step 1 diet for 8 weeks. Serum total cholesterol decreased by 5% and LDL cholesterol by 7% in the psyllium group ($P<.0001$ vs cellulose).

Psyllium consumption of 7 or 10.5 g per day for 12 weeks in addition to a standard cholesterol-lowering diet reduced total cholesterol by 6% and LDL cholesterol by 9% in moderately hypercholesterolemic patients.[31] Respective decreases in the group consuming the diet alone with a sucrose placebo were 3% and 4%. This randomized, double-blind, placebo-controlled trial with an 8-week diet-only run-in enrolled 340 patients with mild to moderate hypercholesterolemia. During the subsequent 12-week double-blind period, psyllium and diet reduced LDL-cholesterol levels by 11% to 13% and total cholesterol levels by 8% to 9% in some patients. In both psyllium groups, the total cholesterol reduction was significantly different from that in the placebo group. The HDL:LDL ratio rose significantly from baseline in all three groups (intention-to-treat population) and in both per-protocol psyllium groups. Psyllium was well tolerated, although a few patients developed minor gastrointestinal side effects. Of 26 patients who withdrew from the three groups because of adverse effects, 24 reported gastrointestinal complaints.

The effect of psyllium in type 2 diabetes was tested in a double-blind, placebo-controlled study[32] with a 6-week run-in period of dietary counseling followed by 6 weeks of treatment with 15 g of psyllium daily or a placebo containing cellulose. Addition of psyllium to the diet significantly decreased total cholesterol by 7% from baseline (vs 4% with placebo) and lowered LDL cholesterol by 16% (vs 9% with placebo). HDL levels improved by 50% in the psyllium group and remained unchanged in the placebo group. The observed lipid-lowering effects of psyllium corroborated findings from most previous studies in type 2 diabetes.

A comparison of psyllium and oat bran with a wheat bran is described below.

Oat Bran Beta Glucan

Oat is the most concentrated source of beta glucan, a high-molecular-weight nonstarch polysaccharide composed of linked glucose units. In 1997 the FDA allowed oat bran to be registered as a cholesterol-reducing food at dosages of 3 g of beta glucan daily.[4] Table 4 summarizes the results of studies with different oat products.

The effect of soluble fibers from oat bran and psyllium was compared with that of a wheat bran placebo.[33] Thirty-six normocholesterolemic men from northern Mexico and 30 hypercholesterolemic men were assigned to three different groups consuming 1.7 g of soluble fiber from psyllium, 2.8 g of soluble fiber from oat bran, or wheat bran as a placebo for 8 weeks. In normocholesterolemic men, the reduction in serum total cholesterol from baseline to treatment end was 10% larger with psyllium and 14% larger with oat bran than with placebo; respective decreases in LDL cholesterol were 17% and 26% (P=NS, between active treatments). The LDL:HDL ratio fell by 29% after psyllium, 38% after oat bran, and by 20% after the control diet. Hypercholesterolemic men had greater reductions than normolipidemic men in almost all respects: serum total cholesterol (psyllium, –18%; oats, –23%), LDL cholesterol (–29%, –34%), and LDL:HDL ratio (–34%, –30%). Of note, however, the control group had lower total and LDL-cholesterol levels at baseline than the other groups, and all participants initially received the same low-fat diet with soluble fibers.

Table 4—Effects of Oats on Blood Lipids

Dose/d	Lipid Parameter, mM: Total Cholesterol Initial	Total Cholesterol End	Total Cholesterol % Change	Triglycerides Initial	Triglycerides End	Triglycerides % Change	LDL Cholesterol Initial	LDL Cholesterol End	LDL Cholesterol % Change	HDL Cholesterol Initial	HDL Cholesterol End	HDL Cholesterol % Change	LDL:HDL Ratio: Treatment Initial	Treatment End	Treatment % Change	Placebo Initial	Placebo End	Placebo % Change	Study Duration, wk	Time to Maximum Effect, wk	No. of Participants
2.8 g soluble fiber from oat bran[33*]	5.53 ±0.34	4.76 ±0.57	−14†	2.64 ±2.11	2.78 ±1.10	+5	3.62 ±1.11	2.66 ±0.85	−26†	0.70 ±0.18	0.83 ±0.21	+16	5.20	3.40	−35†	(control, wheat bran) 3.00	2.40	−20†	8	NR	Treatment, 22 Control, 24
	7.21 ±0.72	5.56 ±0.93	−23†	2.96 ±2.19	2.12 ±1.58	−28†	5.09 ±1.34	3.78 ±1.37	−26†	0.78 ±0.10	0.83 ±0.18	+6†	6.60	4.60	−30†	4.30	3.60	−16†			
84 g oat bran[34*]	7.19 ±0.48	6.25 ±0.58	−15†	1.70 ±0.92	1.61 ±1.03	−5†	5.03 ±0.32	4.19 ±0.50	−17†	1.37 ±0.42	1.33 ±0.33	−3†	4.01	3.32	−17	(control, rice starch) 4.20	4.05	−4†	6	NR	Treatment, 13 Control, 17
2.1 g β-glucan (oat fiber)[35‡]	5.47 ±0.19	4.95 ±0.19	−10†	1.18 ±0.11	1.15 ±0.11	−2†	3.65 ±0.16	3.11 ±0.16	−15†	1.29 ±0.09	1.34 ±0.10	+4†	2.83†	2.32†	−18†	No changes (baseline vs control; control, maintenance diet)			5	NR	23
8.7 g β-glucan	5.47 ±0.19	4.67 ±0.19	−15†	1.18 ±0.11	1.28 ±0.11	+8†	3.65 ±0.16	2.89 ±0.16	−21†	1.29 ±0.09	1.19 ±0.09	−8†	2.83†	2.43†	−14†						
0.75 g oat milk initially with 3.8 g β-glucan (8.8 g dietary fiber)[36*]	6.42 ±0.66	6.25 ±0.67	−3	1.57 ±0.74	1.67 ±0.67	+6	4.35 ±0.65	4.14 ±0.56	−5	1.43 ±0.51	1.37 ±0.33	−5	3.30	3.16	−4†	(control, drink diet) 3.42	3.32	−3†	5	NR	52
20 g oat bran containing 3 g β-glucan[37*]	6.40 ±0.7	6.30 ±0.8	−2†	1.40 ±0.6	1.50 ±0.7	+7†	4.30 ±0.6	4.20 ±0.7	−2†	1.50 ±0.4	1.40 ±0.5	−7†	2.87†	3.00†	+6†	(control, wheat bran) 2.87†	2.80†	−2†	12	8–12	31, each group
9 g β-glucan (oat gum)[38‡]	3.74 ±0.69	4.06 ±0.63	+9†	0.77 ±0.74	0.84 ±0.21	+9†	2.49 ±0.58	2.73 ±0.55	+10†	1.09 ±0.22	1.19 ±0.22	+7	2.28†	2.33†	+2†	No changes (baseline vs control; control, normal diet)			2	NR	14
34 g oat bran containing 9 g β-glucan[39‡]	5.30 ±0.11	4.56 ±0.11	−14†	2.14 ±0.16	2.03 ±0.16	−5†	3.36 ±0.12	2.59 ±0.12	−23†	0.96 ±0.05	1.04 ±0.05	+8†	3.50†	2.49†	−29†	No changes (baseline vs control; control, white bread)			12	NR	8 diabetic men

NR=not reported.
*Initial values from baseline values after randomization.
†Calculated from published data.
‡Initial values from control diet.

In a 6-week randomized, double-blind, parallel-group trial,[34] 44 adults with hypercholesterolemia were assigned to one of three groups: 84 g of an oat bran product daily (n=13); a rice bran product (n=14); or rice starch placebo (control) (n=17) in conjunction with their usual low-fat diet (similar to the AHA step 1 diet). Serum cholesterol decreased significantly by 13% in the oat bran group but remained unchanged in the control group. This result was attributable to a reduction of 17% in LDL cholesterol in the oat bran group, which also experienced a significant 17% drop in the LDL:HDL ratio.

A randomized crossover study of 23 mildly hypercholesterolemic volunteers who consumed self-selected diets found a significant dose-response effect on total cholesterol from beta-glucan concentration in oat extracts.[35] A maintenance diet was served for 1 week before the study period. The same 7-day menus—containing an oat fiber extract with a daily supplement of 2.1 or 8.7 g of beta glucan—were then served for the next 5 weeks. Half of the participants were on a fiber diet and were switched from one to the other for the following 5 weeks. Consumption of beta glucan had a significant effect. Compared with baseline values, total cholesterol decreased by 10% with 2.1 g and by 15% with 8.7 g; respective reductions in LDL cholesterol were 15% and 21%. The difference between low and high beta-glucan doses was significant for total cholesterol but not for LDL cholesterol. The LDL:HDL ratio was reduced by 14% to 18% in the two groups. HDL and triglyceride levels did not change significantly.

A randomized, double-blind crossover trial in 52 mildly hypercholesterolemic men compared 0.75 L of oat milk with 3.8 g of beta glucan with a control rice drink.[36] After 5 weeks of one regimen, the groups consumed the other diet for 5 weeks, with a 5-week washout between. Oat milk consumption significantly reduced total and LDL cholesterol (both 6%), although the reductions were slightly smaller (total cholesterol 3%, LDL cholesterol 5%) compared with baseline levels. The LDL:HDL ratios did not significantly differ after the two drinks. On further analysis, the higher the initial serum LDL level, the more pronounced the lipid-lowering response after oat milk.

Daily intake of 3 g of beta glucan did not significantly reduce total and LDL-cholesterol concentrations in mildly hypercholesterolemic patients in a double-blind, placebo-controlled, randomized, parallel-group study.[37]

A metabolically controlled, randomized, single-blind crossover study[38] recruited 14 healthy young men from a university's staff and students to test the effect of 9 g of beta glucan daily in instant whip or a placebo instant whip after a 1-week run-in. No significant decrease in total and LDL cholesterol or triglycerides occurred after the consumption of oat gum, but HDL cholesterol rose by a significant 6% and the LDL:HDL ratio by 2%.

The long-term effect of oat bran–concentrated bread was evaluated in a 24-week crossover study of eight men with type 2 diabetes (mean age, 45 years).[39] Four randomly chosen men consumed oat bran products providing 9 g of soluble fiber per day; the others had white bread first. After 12 weeks, participants switched directly to the other diet. Consumption of oat bran had a significant effect, producing decreases of 14% in total cholesterol, 23% in LDL cholesterol, and 24% in the LDL:HDL ratio.

Effect of Plant Sterols and Stanol Esters on Blood Lipids

With the exception of substitutions at the C24 position of the side chain, plant sterols are structurally similar to cholesterol. In the 1970s, beta sitosterol was approved as a cholesterol-lowering drug for human use. The cholesterol-reducing properties of these substances are believed to result from displacement of cholesterol from micelles. Plant sterols are not synthesized in humans; they are absorbed poorly or not at all and are then transported to the liver and excreted in the bile.

The most frequently used plant sterols are campesterol, beta sitosterol, and stigmasterol. Hydrogenation of the delta-5 double bond of plant sterols forms plant stanols, such as sitostanol and campestanol. Like plant sterols, plant stanols are not easily incorporated into foods, but esterification with food-grade fatty acids increases their solubility in dietary fats.[40] A typical western diet reportedly contains from 160 to 360 mg of phytosterols per day.[41,42] In 2000 the FDA accepted the claim that plant stanol and sterol esters had heart-healthy effects.[6] Margarines and spreads rich in phytosterol or stanol esters have been formulated, and their effect on serum cholesterol concentrations has been widely studied. Table 5 summarizes the results of these studies.

A 1-year randomized, double-blind, parallel-group study evaluated sitostanol in 153 patients with mild hypercholesterolemia.[42] The control group of 51 consumed margarine without sitostanol ester; the treatment group of 102 consumed margarine containing 1.8 or 2.6 g of sitostanol ester daily. At the beginning of a 6-week run-in period, patients replaced 24 g per day of their normal dietary fat with a margarine containing rapeseed oil in an *ad libitum* diet. The control group continued to use normal dietary fat. Daily consumption of sitostanol 2.6 g significantly decreased serum LDL-cholesterol levels at 6 months (12%) and 12 months (16%) compared with the control group (+1% and −1%). The LDL:HDL ratio fell by a significant 16% after 1 year of treatment. Daily consumption of 1.8 g of sitostanol during the second half of the test period did not change the LDL-cholesterol concentration. Neither serum triglycerides nor HDL cholesterol was affected by sitostanol, but the HDL:LDL ratio rose by a significant 20%. The authors concluded that, for practical purposes, the two dosages had similar cholesterol-lowering effects. The sitostanol ester margarine was well tolerated.

A 1-week metabolic study[43] in 11 colectomized patients consuming 25 g of margarine with 2 g of stanols per day showed effective inhibition of cholesterol absorption and reduction of serum cholesterol concentrations occurring within 1 day of the start of stanol ester consumption and increasing during the test period. Plant stanols were secreted by the bile.

The effect of plant stanol ester spread was compared with a placebo spread in 67 women and 100 men who took statins for at least 90 days and still had LDL-cholesterol levels of 3.36 mM or higher.[44] For 8 weeks, the patients consumed 24 g of spread containing 3 g of stanols from canola oil or a placebo while maintaining their usual diet; statin therapy continued. Both spreads were well tolerated. The stanol spread lowered LDL cholesterol at 8 weeks by 17%, compared with a 7% reduction in the placebo group. At 2 and 4 weeks, reductions in LDL- and total cholesterol concentrations were also greater with stanols than with placebo. The LDL:HDL ratio decreased by 11% compared with 5% in the placebo group. HDL cholesterol and serum triglycerides did not change significantly.

Table 5. Effects of Plant Sterols and Stanol Esters on Blood Lipids

Dose/d	Lipid Parameter, mM: Total Cholesterol Initial	End	% Change	Triglycerides Initial	End	% Change	LDL Cholesterol Initial	End	% Change	HDL Cholesterol Initial	End	% Change	LDL:HDL Ratio Treatment Initial	End	% Change	Placebo Initial	End	% Change	Study Duration, wk	Time to Maximum Effect, wk	No. of Participants
24 g margarine containing 2.6 g sitostanol[42]	6.05 ±0.10	5.43 ±0.13	−10†	1.25 ±0.07	1.23 ±0.06	−2*	4.14 ±0.10	3.47 ±0.08	−16†	1.37 ±0.05	1.37 ±0.03	0	3.02†	2.53†	−16†	Normal diet control, placebo spread 3.00†	2.91†	−3*	1 y	1 y	Treatment, 102 Control, 51
25 g margarine containing 2 g stanol[43]	5.31 ±0.33	4.43† ±0.27	−17†	2.17 ±1.27	1.10† ±0.96	−49†	2.53 ±0.24	2.18† ±0.15	−14†	1.49 ±0.12	1.47† ±0.06	−1*	1.70†	1.48†	−13†	Noncontrolled study			1	1	11 (colectomized)
24 g margarine containing 3 g plant stanol[44]	6.00 ±0.72	5.30† NR	−12	1.83 ±0.69	1.81† NR	−2	3.80 ±0.65	3.15 NR	−17	1.34 ±0.36	1.33† NR	−1	2.83	2.37	−16†	Placebo spread 2.81†	2.65†	−6†	8	8	Treatment, 84 (all treated with statins) Control, 83
25 g margarine containing 2.34 g plant stanols[45a]	6.55 ±0.78	5.34 ±0.76	−18†	1.45 ±0.70	1.26 ±0.67	−14†	4.54 ±0.72	3.48 ±0.77	−23†	1.44 ±0.38	1.41 ±0.33	−2*	3.15†	2.47†	−22†	Low-fat diet 3.14†	2.79†	−11†	8	8	Treatment, 18, 20 Control, 17
	6.13 ±0.81	5.15 ±0.78	−16†	1.24 ±0.50	1.13 ±0.45	−9*	4.25 ±0.85	3.45 0.76	−19†	1.41 ±0.38	1.36 ±0.31	−4*	3.01†	2.54	−16†						
25 g margarine with 1.6 g stanols[46a]	6.51 ±1.03	6.06 ±0.98	−7*	1.40 ±0.65	1.26 ±0.63	−10*	4.42 ±0.95	4.15 ±0.87	−6*	1.51 ±0.30	1.52 ±0.31	+1*	2.93†	2.73†	−7†	No changes (baseline vs control values; control, placebo spread)			4	NR	22
25 g margarine with 2.4 g stanols	6.51 ±1.03	6.06 ±0.92	−11†	1.40 ±0.65	1.29 ±0.64	−8†	4.42 ±0.95	3.95 ±0.75	−11†	1.51 ±0.30	1.50 ±0.37	−1*	2.93†	2.63†	−10†	No changes (baseline vs control values)			4	NR	22
25 g margarine with 3.2 g stanols	6.15 ±1.03	5.75 ±0.78	−12†	1.40 ±0.65	1.16 ±0.56	−17†	4.42 ±0.95	3.91 ±0.69	−12†	1.51 ±0.30	1.50 ±0.32	−1*	2.93†	2.61†	−11†	No changes (baseline vs control values)			4	NR	22
Campestanol ester–rich margarine, 3.18 g stanols in 25 g margarine[47a]	6.06 ±0.16	5.71 ±0.18	−6†	1.21 ±0.14	1.15 ±0.12	−5*	3.98 ±0.14	3.58 ±0.17	−10†	1.54 ±0.09	1.62 ±0.09	+5†	2.80	2.42	−14†	No change (baseline vs control values; control, home diet)			6	NR	23
Sitostanol ester–rich margarine, same dose	6.06 ±0.16	5.79 ±0.17	−4*	1.21 ±0.14	1.18 ±0.13	−2*	3.98 ±0.14	3.62 ±0.14	−9†	1.54 ±0.09	1.63 ±0.10	+6†	2.80	2.44	−13†	No change (baseline vs control values; control, home diet)			6	NR	23
~ 3 g phytosterol from soybean oil in 30 g margarine/d[48b]	5.18 5.11– 5.26	4.75 4.68– 4.82	−8	1.10 1.06– 1.16	1.10 1.05– 1.15	0	3.36 3.29– 3.43	2.92 2.86– 2.99	−13	1.25 1.22– 1.27	1.25 1.23– 1.27	0	2.69†	2.34†	−13*	No changes (baseline vs control values)			3.5	NR	100

Continued

Table 5. Effects of Plant Sterols and Stanol Esters on Blood Lipids (cont'd)

	Lipid Parameter, mM												LDL:HDL Ratio								
	Total Cholesterol			Triglycerides			LDL Cholesterol			HDL Cholesterol			Treatment			Placebo			Study Duration, wk	Time to Maximum Effect, wk	No. of Participants
Dose/d	Initial	End	% Change	Initial	End	% Change	Initial	End	% Change	Initial	End	% Change	Initial	End	% Change	Initial	End	% Change			
Margarine containing stanol ~3 g[48§]	5.18	4.81	−7	1.10	1.15	+5[†]	3.36	2.96	−13	1.25	1.25	0	2.69[†]	2.37[†]	−12[†]	No change (baseline vs control values)			3.5	NR	100
	5.11–5.26	4.73–4.88		1.06–1.16	1.10–1.21		3.29–3.43	2.89–3.02		1.22–1.27	1.23–1.27										
Sitostanol 1.84 g in 24 g margarine[49†]	6.37 ±0.18	5.71 ±0.18	−10	2.39 ±0.20	1.86 ±0.16	−17	4.35 ±0.23	3.95 ±0.19	−8	0.92 ±0.05	0.93 ±0.05	+1	4.73[†]	4.25[†]	−10[†]	4.55[†]	4.54[†]	−1[†]	3	NR	15
β-sitosterol, same dose	6.39 ±0.18	5.49 ±0.15	−13	2.52 ±0.21	1.98 ±0.21	−19	4.29 ±0.25	3.66 ±0.15	−13	0.99 ±0.06	0.93 ±0.16	−6	4.33[†]	3.94[†]	−9[†]	4.55[†]	4.54[†]	−1[†]			
1.5 g phytosterol in 30 g margarine[50*]	6.73 ±1.15	5.42 ±0.92	−19[†]	3.33 ±1.23	3.00 ±1.60	−10[†]	4.45 ±1.37	3.37 ±0.94	−24[†]	0.75 ±0.24	0.67 ±0.18	−11[†]	5.93[†]	5.03[†]	−15[†]	7.81[†]	7.60[†]	−3[†]	4		16, each group
3 g sitostanol packed in gelatin capsules[51§]	6.18 ±0.75	6.15 ±0.80	0	1.65 ±0.62	1.67 ±0.54	+1[†]	4.52 ±0.67	4.44 ±0.80	−2[†]	1.01 ±0.28	1.06 ±0.31	+5[†]	4.48[†]	4.19[†]	−6[†]	No changes (baseline vs control values; control, AHA Step 1 diet)			3 mo	NR	33
1.61 g plant sterol in 25 g margarine[52*]	5.16 ±0.94	4.84 ±0.92	−6	1.13 ±0.62	1.05 ±0.47	−7[†]	3.05 ±0.85	2.77 ±0.76	−9	1.64 ±0.40	1.63 ±0.41	−1	1.86[†]	1.70[†]	−9[†]	No changes (baseline vs control values)			3.5	NR	100
8.6 g phytosterol in 40 g margarine[53*]	4.88 ±0.46	4.07 ±0.46	−17[†]	NR	NR	NR	3.18 ±0.49	2.52 ±0.45	−21[†]	1.26 ±0.29	1.15 ±0.26	−9[†]	2.52[†]	2.19[†]	−13[†]	2.39[†]	2.27[†]	−5[†]	3–4	NR	Treatment, 10 Control, 11

NR=not reported.
*Initial values from baseline values after randomization.
†Calculated from cited published data.
‡Baseline after 4-week high-fat run-in diet.
§Initial values from control diet.

The effect of plant stanol ester–containing margarine was studied in 55 mildly hypercholesterolemic patients consuming a low-fat, low-cholesterol diet.[45] After a 4-week high-fat diet, participants were randomly assigned to 25 g of margarine with 2.34 g of wood stanol (sitostanol 2.15 g, campestanol 0.19 g) or 2.20 g of vegetable stanols from soy oil (sitostanol 1.50 g, campestanol 0.70 g) or a diet without stanols for 8 weeks. During the study, the diet resembled the NCEP step 2 diet. At 8 weeks, serum LDL cholesterol decreased by 14% with wood stanol and 9% with vegetable stanols compared with the control diet. Respective reductions in total cholesterol were 11% and 8%. The decline in the LDL:HDL ratio exceeded that in the control group by 11% with wood stanol and by 5% with vegetable stanol. Consumption of plant stanols was deemed to offer an additional, clinically significant reduction in cholesterol concentrations compared with that of a low-fat diet alone.

Plant stanol esters affected serum cholesterol concentrations in a dose-dependent manner in 22 hypercholesterolemic patients who received different dosages of plant stanol esters added to margarine.[46] Throughout the study, participants ate a standardized background diet with precise amounts and qualities of fat. After a 1-week run-in, all patients consumed five different doses of plant stanol (0.8, 1.6, 2.4, 3.2 g, and control dose) daily for 4 weeks each. A 1.6-g dose significantly reduced total (7%) and LDL (6%) cholesterol. Increasing the dose to 2.4 and 3.2 g had no clinically important additional effects. The LDL:HDL ratio decreased by 7% with 1.6 g, 10% with 2.4 g, and 11% with 3.2 g. Doses above 2.0 to 3.0 g of stanol produced no additional effect.

The efficacy of different plant campestanol/sitostanol mixtures in combination with margarine or butter was investigated through a comparison of their effect on serum lipid concentrations.[47] Twenty-three mildly hypercholesterolemic postmenopausal women replaced 25 g of their normal dietary fat in their *ad libitum* daily diet with sitostanol ester–rich margarine (3.18 g of stanols with 82.8% sitostanol, 7.5% campestanol from tall oil) or campestanol ester–rich margarine (3.16 g of stanols with 65.2% sitostanol and 28.1% campestanol). The 6-week margarine periods were double-blinded in random order and used a crossover design. Campestanol ester–rich margarine decreased total cholesterol by 4% to 6% and LDL cholesterol by 9% to 10%, making it as effective as a sitostanol ester–rich margarine with a low campestanol content. The LDL:HDL ratio decreased significantly by 13% to 14%. HDL cholesterol increased significantly with the sitostanol ester–rich margarine and with butter alone when compared with the home diet. Butter and the stanol ester–enriched margarines did not differ in their HDL-increasing effect.

Sitostanol ester and vegetable oil sterol ester were also compared by way of a randomized, double-blind, placebo-controlled, incomplete Latin-square design with five treatments and four periods of 3.5 weeks each.[48] One hundred normocholesterolemic or mildly hypercholesterolemic individuals replaced their usual spread with 30 g of margarine daily containing approximately 3 g of stanols or 3 g of plant sterols from soybean oil. Both treatments lowered total and LDL concentrations similarly (8%–13%), compared with the control preparation, without affecting HDL cholesterol. The LDL:HDL ratio dropped significantly by 10% to 13%. Plasma sitosterol and campesterol levels were significantly higher for soybean oil sterol margarine and significantly lower for stanol ester margarine than for controls. Margarines enriched with sterols from rice bran or shea nut did not differ from the control.

A randomized, crossover, double-blind trial compared margarines containing plant sterol esters with margarines containing saturated plant stanol esters in terms of their effect on serum lipids.[49] Fifteen mildly hypercholesterolemic men consumed a fixed-intake North American solid-food diet during the 21-day treatment period, each period followed by a 5-week washout; 23 g of margarine with 1.84 g of plant sterols or stanols from vegetable oil was taken daily. The LDL:HDL ratio decreased by 9% (sterols) and 10% (stanols). The stanol group saw a more pronounced decline than the sterol group in total (13% vs 10%) and LDL cholesterol (13% vs 8%), and both groups posted greater decreases than the control group (total cholesterol 6%, LDL cholesterol 4%). These results differ from those in the sitostanol/vegetable oil sterol ester study,[48] which found no differences; that outcome may be attributed to aspects of study design including phytosterol formulation, dosage, or dietary composition.

The effect of sitostanol-containing phytosterols from tall oil on plasma lipids was investigated in a randomized, double-blind trial.[50] For 30 days, 32 hypercholesterolemic men consumed a diet that reflected the nutrient intake recommended by Health and Welfare Canada. The control group received this diet alone; the test group also consumed 30 g of margarine with 1.7 g of phytosterols daily. The LDL-cholesterol concentration dropped by a significant 9% on the diet alone and by a significant 24% on the phytosterol-enriched diet, significantly higher than that of the control group. Respective reductions in total cholesterol were 10% and 20%, although the differences were not significant when compared with baseline values. The LDL:HDL ratio decreased by 15% with the enriched diet and by 3% with the control diet.

These results contrast with those in a test of the cholesterol-lowering effects of dietary supplementation with sitostanol from tall oil (3 g/d packed in capsules each containing 250 mg of sitostanol and 1 g of safflower oil) in 33 men with mild hypercholesterolemia whose dietary cholesterol was restricted to less than 200 mg/d (step 1 diet).[51] Each test period lasted 3 months. Sitostanol added to the step 1 diet had no significant effect on total or LDL cholesterol compared with the step 1 diet alone. Despite differences in study design and compliance, the authors of another study[49] assumed that the capsular phytosterols may not fully disperse or dissolve in the intestines before absorption, limiting their ability to reduce cholesterol absorption.

A randomized, double-blind, placebo-controlled, balanced, Latin square–designed study[52] investigated 100 normocholesterolemic and mildly hypercholesterolemic volunteers who each consumed four spreads with different levels of plant sterols for 3.5 weeks (control, 0.83, 1.61, 3.24 g of plant sterol from vegetable oil, mainly soybean). Compared with the control spread, the three dosages of plant sterols reduced total cholesterol by 5% to 7% and LDL cholesterol by 7% to 10%; the differences among the dosages were not statistically significant. The LDL:HDL ratio decreased by a significant 9%.

A safety evaluation in 12 healthy men and 12 healthy women was conducted to determine the effect of phytosterol ester consumption on serum lipid levels and viable fecal microflora count, fecal bacterial enzyme activities, and female sex hormones.[53] In part 1, participants consumed 40 g of control margarine under controlled dietary conditions for 21 and 28 days; in part 2, participants were randomly allocated to consume 40 g daily of either the control or the test margarine containing 8.6 g of vegetable oil phytosterols. Compared with the control group, the phytosterol group experienced significant reductions in total (18%) and LDL cholesterol (23%), in fecal lactic acid concentration, and in serum progesterone levels. The LDL:HDL ratio fell significantly by 13% (vs 5% in the control group). Total fecal aerobes, lactobacilli, and staphylococci

were also significantly reduced in the control group; in the test group, only the lactobacillus count decreased. None of the significant findings except the beneficial reduction of serum lipids were considered to be biologically important.

Effect of Garlic on Blood Lipids

Three meta-analyses are reviewed. Two early meta-analyses of published clinical trials of garlic revealed statistically significant reductions of 9% to 12% in total cholesterol concentrations.[54,55] A more recent meta-analysis[56] involved 13 studies of 781 patients. Only randomized, double-blind, placebo-controlled studies were included in our review; total cholesterol levels had to be at least 5.17 mmol/L. A significant difference ($P<.01$) in the reduction of total cholesterol levels from baseline favored garlic over placebo. The weighted mean difference of –0.41 mmol/L (95% confidence interval, –0.66 to –0.15 mmol/L) was equivalent to a 6% reduction from baseline.

A parallel study investigated the effect of dried garlic-powder tablets on blood lipids (Table 6).[57] The active-treatment group consisted of Europeans with a fasting cholesterol concentration from 6.0 to 8.5 mmol/L and an LDL concentration of at least 3.5 mmol/L. At the end of the 6-month trial, no significant differences were observed between the treatment and control groups.

Comparable results were obtained from a crossover study of individuals with mild to moderate hypercholesterolemia who took 300 mg of garlic-powder tablets three times daily for 12 weeks.[58] No significant differences were recorded between the garlic and placebo periods on any of the blood parameters measured.

In a parallel-group study,[59] patients with coronary artery disease (30 patients in each group) received two capsules twice daily; each capsule contained ethyl acetate extract from 1 g of peeled and crushed raw garlic. Significant net reductions occurred in total serum cholesterol (11%) and triglycerides (12%) after the 3-month treatment; HDL cholesterol rose significantly (22%).

The efficacy of supplementation with aged garlic extract was investigated in an intervention study in 34 men with cholesterol concentrations between 5.7 and 7.4 mmol/L.[60] The patients were divided into two groups and received either nine capsules of aged garlic extract 800 mg per capsule daily or placebo (each placebo capsule contained 800 mg of a common food ingredient). After 5 months, plasma total and LDL-cholesterol concentrations had decreased by 7% and 10%, compared with placebo. Plasma triglyceride and HDL-cholesterol levels remained constant.

Two doses of a commercial garlic preparation were tested in 52 moderately hypercholesterolemic adults (LDL cholesterol 3.36–4.91 mM, triglycerides <3.39 mmol/L) who received either 500 or 1000 mg of dehydrated garlic powder daily or placebo.[61] No significant differences were observed in any of the lipids. Results were comparable in moderately hypercholesterolemic patients with LDL-cholesterol levels between 3.88 and 5.17 mmol/L.[62] Lipid parameters did not change significantly in either the active-treatment or placebo group.

In contrast, the efficacy of a garlic preparation on hypercholesterolemia was confirmed in renal transplant recipients.[63] Patients with levels of LDL cholesterol in excess of 4.14 mmol/L, total cholesterol higher than 6.2 mmol/L, and triglycerides of 5.65 mmol/L or less were studied. Garlic decreased total and LDL-cholesterol levels after 6 weeks of therapy, and the levels remained stable at 12 weeks; no significant changes were observed with placebo.

Table 6. Effect of Garlic on Blood Lipids

Dose/d	Lipid Parameter, mM: Total Cholesterol Initial	Total Cholesterol End	Total Cholesterol % Change	Triglycerides Initial	Triglycerides End	Triglycerides % Change	LDL Cholesterol Initial	LDL Cholesterol End	LDL Cholesterol % Change	HDL Cholesterol Initial	HDL Cholesterol End	HDL Cholesterol % Change	LDL:HDL Ratio: Treatment Initial	Treatment End	Treatment % Change	Placebo Initial	Placebo End	Placebo % Change	Study Duration, wk	Time to Maximum Effect, wk	No. of Participants
Odor-controlled garlic tablets 3×300 mg[57]	6.96 ±0.57	6.91 ±0.67	−1†	1.70 ±(1.32;+(1.06; 2.18)	1.58 2.32)	−7†	4.96 ±0.62	4.94 ±0.71	−0.4†	1.15 ±0.30	1.17 ±0.31	+2†	4.31†	4.22‡	−2†	(lactose tablet impregnated with garlic powder)‡ 4.41†	4.48†	+2†	24	NR	Treatment, 57 Control, 58
Garlic powder 3×300-mg tablets[58]*	6.72 ±0.65	6.54 ±0.54	−3†	1.53 ±0.63	1.47 ±0.59	−4†	4.76 ±0.54	4.64 ±0.52	−3†	1.26 ±0.37	1.23 ±0.38	−2†	3.78†	3.77†	0.3†	(lactose tablets)¶ 3.78†	3.77†	−0.3†	12	NR	30
2×2 garlic oil capsules (1 capsule=1 g fresh garlic)[59]*	6.54 ±0.17	5.70 ±0.18	−13†	1.47 ±0.07	1.24 ±0.05	−16†	NR	NR	NR	1.05 ±0.03	1.28 ±0.04	+22†	NR	NR	NR	(placebo; no details reported)			12	12	Treatment, 30 Control, 30
9×1 capsules (1 capsule=800 mg AGE)[60]*	6.36 ±0.13	5.90 ±0.13	−7†	NR	NR	NR	4.19 ±0.10	3.75 ±0.10	11†	NR	NR	NR	NR	NR	NR	(placebo capsules with common food ingredients)			20	20	Treatment, 17 Control, 17
3×1 tablet (1 tablet= 333 mg garlic powder)[61]*	6.08 ±0.70	5.82 ±0.59	−4†	1.42 ±0.63	1.34 ±0.59	−6†	4.22 ±0.47	3.96 ±0.57	−6†	1.19 ±0.31	1.27 ±0.36	+7†	3.54†	3.12†	−12†	(placebo tablets with matrix only) 3.43†	3.29†	−4†	12	12	Treatment, 16 Control, 18
3×1 tablet (1 tablet= 300 mg garlic powder)[62]*	6.47 ±0.75	6.40 ±0.68	−1†	1.64 ±0.61	1.59 ±0.49	−3†	4.37 ±0.65	4.33 ±0.66	−1†	1.33 ±0.30	1.32 ±0.17	−1†	3.29†	3.27†	−1†	(placebo; no details reported) 3.12†	3.05‡	−2†	12	NR	25, each group
2×1 tablet (1 tablet= 680 mg garlic)[63]*	7.50 ±0.21	7.11 ±0.23	−5†	2.56 ±0.20	2.75 ±0.28	+7†	4.99 ±0.21	4.70 ±0.21	−6†	1.55 ±0.10	1.47 ±0.10	−5†	3.22†	3.19†	−1†	(placebo; no details reported) 4.00†	4.49‡	+12†	12	12	35 renal transplant patients

NR=not reported, AGE=aged garlic extract.
*Initial values from control diet.
†Calculated from cited published data.
‡Initial values from baseline values after randomization.

Garlic powder was investigated in a 12-week double-blind, randomized, placebo-controlled, two-center study of 50 patients with mild hypercholesterolemia.[64] Mean LDL and triglyceride levels less than 4 mmol/L following 8 weeks of stabilization on the NCEP step 1 diet were required for randomization. No differences in cholesterol levels were found between the placebo and treatment groups. The most common side effects were garlic breath or a change in body odor. This study is not included in Table 6 because of insufficient data.

DISCUSSION

The analysis included 7 clinical trials investigating the influence of ISP on serum lipid levels. The review covered 5 trials of psyllium, 7 of oats, 12 of plant stanols and sterol esters, and 7 studies of garlic preparations. These results were compared with those of 4 studies of Abacor (3) and Abalon (1).

The amount of soy protein ingested daily ranged from 20 to 85 g. These 4- to 24-week trials reported significant reductions in serum LDL cholesterol (range, 4%–21%) and consequently in LDL:HDL ratios (range, 3%–27%) compared with control (+6% to –19%). The Abacor and Abalon studies reported LDL-lowering effects in the range of 8% to 21% (4%–9% net), with the LDL:HDL ratio decreasing by 10% to 27%, compared with decreases of 4% to 19% in the placebo group. In the seven trials, as well as in the four studies with Abacor and Abalon, the total cholesterol-lowering effect of ISP was significant, from 3% to 6% (net), compared with placebo. The four studies that demonstrated nonsignificant changes in total cholesterol included mostly normocholesterolemic[20,21] or mildly hypercholesterolemic participants.[16] Only one trial in moderately hypercholesterolemic patients[19] noted no significant decrease in total cholesterol. Among the reviewed trials, only one study[16] showed a significant increase in HDL cholesterol. Abalon was the only product tested that significantly reduced triglycerides compared with products containing ISP.[14]

Compared with the other soy products, Abacor and Abalon substantially affected cholesterol levels. In only one study[16] were results nearly comparable overall and net changes in HDL cholesterol and the LDL:HDL ratio superior to those with Abalon[14]; however, the net changes in total and LDL cholesterol and triglycerides were lower than those reported for Abalon and some Abacor preparations.

Soy protein reduces the serum LDL-cholesterol concentration even when administered as an adjunct to controlled low-cholesterol regimens such as the NCEP step 1 diet.[15,16,19] A review of 38 trials[10] showed that the ability of soy protein to lower lipid levels was related to the initial level of serum cholesterol, the only significant predictor of the change in serum lipid concentrations. Normocholesterolemic and mildly hypercholesterolemic patients (≤6.6 mM) achieved nonsignificant reductions in the range of 3% to 4%. Those with moderate hypercholesterolemia (6.7–8.6 mM) achieved significant decreases (mean, 7%), and patients with severe hypercholesterolemia, whose initial total cholesterol levels exceeded 8.66 mmol/L, demonstrated reductions of 20%. The pattern of LDL decrease was similar, and changes in HDL cholesterol were uniformly nonsignificant in this meta-analysis.

It is not known which bioactive component of soy protein mediates changes in lipid levels, and the mechanism of the lipid-lowering effect of soy protein remains unclear. There are differences in the amino-acid composition of soy and animal proteins. Soy protein is richer in L-arginine, and its isoflavones may also contribute to

the lipid-lowering activity. Soy isoflavones are nonsteroidal compounds from soybeans that have a weak estrogen-like activity and bind to estrogen receptors. Soy isoflavones are composed of three main isoflavones and their glycosylated forms, which also show antioxidant properties. The mechanism of the possible cholesterol-lowering activity of soy isoflavones is still undefined.[65]

Trials that compared isoflavone-free soy protein with soy protein containing fixed levels of isoflavones showed that isoflavones contribute to the lipid-lowering effect in women.[17,20] Significant changes in the concentration of LDL-receptor messenger RNA were observed in blood mononuclear cells after a daily intake of 56 mg (27%) and 90 mg (75%) of isoflavones for 24 weeks; this raised the possibility that isoflavones may trigger estrogen-like enhancement of LDL-receptor activity.[16]

Most of the psyllium trials involved 8 weeks of a controlled cholesterol-lowering regimen, such as the NCEP step 1 diet from the American Heart Association, prior to treatment and featured a parallel-group design. Intake of 10.2 g of psyllium (7 g of soluble fiber) from 6 to 26 weeks produced a net reduction of total cholesterol that ranged from nonsignificant in a long-term study to 5%; LDL decreased by 2% to 7% compared with the diets alone. Three meta-analyses showed an LDL-cholesterol reduction ranging from 6% to 7% following daily consumption of 9.1 to 10.2 g of psyllium (Table 7).[24,28,66]

Two trials[32,33] reported rather large decreases, but lipid reductions were also substantial in the control groups and the participants did not follow a low-fat diet in either study. In one report[33] that noted large differences in initial lipid levels, LDL cholesterol was 22% to 25% lower in the control group than in the treatment group when the study began.

Variable results emerged from the seven clinical trials of beta glucan–containing oat bran (100 g of oat bran contains a mean dry weight of 5.5 g of beta glucan as a base).[67] Intake of high levels of beta glucan (approximately 3.0–8.7 g daily) significantly decreased serum total cholesterol by 2% to 15% and LDL cholesterol by 2% to 26% in mildly to moderately hypercholesterolemic individuals. Soluble fibers did not significantly affect HDL cholesterol and triglycerides. In a very small study[39] of eight patients with type 2 diabetes, 9 g of beta glucan lowered LDL levels by 23%. In young normocholesterolemic men, however, the same daily intake of beta glucan increased serum total and LDL-cholesterol levels by 9%.[38]

One meta-analysis of 67 controlled trials of dietary fiber[24] emphasized the small mean reduction in LDL cholesterol (0.057 mmol/L) per gram of fiber for the 2- to 10-g daily dosage of viscous fiber. No major differences were reported among the different sources of viscous fibers, which did not include soy fibers. The authors concluded that soluble fibers could make only a small contribution to dietary therapy aimed at lowering cholesterol.

A daily intake of 25 g of soy fibers significantly reduced serum total cholesterol (4%) and LDL (5%) in moderately hypercholesterolemic men.[68] Other investigators using different preparations noted variable responses.[69]

Of the 12 investigations of plant stanol and sterol esters, 10 involved mildly hypercholesterolemic volunteers, and 2 enrolled normocholesterolemic individuals. Nearly all studies in which ester-containing margarines and spreads replaced usual spreads reported significant (net) reductions in serum total cholesterol (4%–16%) and LDL cholesterol (4%–18%) after 4 to 12 weeks compared with controls. Triglycerides and HDL levels did not significantly change in the majority of the trials reviewed. Only one study[51] with sitostanol noted no significant reductions in serum lipid levels.

Table 7. Comparison of Meta-Analyses—Effect of Soy, Psyllium, Oats, and Garlic on Blood Lipids

Dose/d	Total Cholesterol Baseline Levels, (mM)	Total Cholesterol mM	Total Cholesterol %	Triglycerides mM	Triglycerides %	Net Changes LDL Cholesterol mM	Net Changes LDL Cholesterol %	HDL Cholesterol mM	HDL Cholesterol %	LDL:HDL Ratio mM	LDL:HDL Ratio %	Study Duration	Subjects, no.	Studies, no.
17–24 g ISP (average, 47 g); 14 studies, ≤31 g[19]	All (3.29–>8.66)	−0.60 (−0.85, −0.35)	−9.3	−0.34 (−0.66, 0)	−10.5	−0.56 (−0.82, −0.29)	−12.9	+0.03 (−0.08, +0.14)	+2.4	NR	NR	NR	743	38
	3.29–5.12	−0.13 (−0.44, +0.17)	−3.3	NR	NR	−0.18 (−0.53, +0.16)	−7.7	NR	NR	NR	NR	NR	NR	NR
	5.20–6.60	−0.26 (−0.56, +0.04)	−4.4			−0.28 (−0.63, +0.07)	−6.8							
	6.71–8.61	−0.47 (−0.96, −0.18)	−7.4			−0.47 (−0.91, −0.03)	−9.8							
	>8.66	−1.85 (−2.24, −1.46)	−19.6			−1.76 (−2.33, −1.19)	−24.0							
4.7–16.2 g psyllium (average, 9.1 g)[34]	6.41±0.68	−0.25* (−0.34, −0.181)	−3.9*	0.027 (−0.06–0.12)	+1.5	−0.26 (−0.41, −0.23)	−5.9*	−0.01 (−0.04, −0.018)	−0.8*	−0.18*	−5.1*	14–112 d (average, 53 d)	279T, 276C (P) 202 (X)	17; 11P, 6X
1.5–13 g oat (average, 5.0 g)[34]	6.31±0.84	−0.19 (−0.26, −0.11)	−3.0*	0.04 (−0.025–0.11)	+2.0	−0.16 (−0.24, −0.13)	−3.6*	−0.01 (−0.04, 0.015)	−0.8*	−0.09*	−2.6*	14–84 d (average, 39 d)	703T, 552C (P) 345 (X)	25; 13P, 12X
10.2 g psyllium AHA step 1 diet[30]	6.14±0.71 (psyllium) 6.23±0.74 (control)	−0.24 ± 0.05	−3.9 ± 0.74	+0.06 ± 0.04	+3.7 ± 2.8	−0.28 ± 0.04	−6.7 ± 0.96	−0.01 ± 0.01	−1.0 ± 1.0	−0.23 ± 0.05	−6.6 ± 1.5	≥8 wk	384T 272C	8
Garlic, depending on formulation[14]	6.42*	−0.77 (−0.65, −0.89)	−12	−0.31 (−0.14, −0.49)	−13	NR	NR	−0.04 (−0.11, 0.03)	NR	NR	NR	1–12 mo	952	16
700–1000 mg garlic[35]	6.93±0.96 (T) 6.85±1.06 (C)	−0.59 (−0.44, −0.74)	−8.5*	NR	NR	NR	NR	NR	NR	NR	NR	8–24 wk	348T, 342P, 345C	5
600–900 mg garlic (powder)[36]	≤5.17	−0.41 (−0.66, −0.15)	−5.8	NR	NR	NR	NR	NR	NR	NR	NR	8–24 wk	781	13
600–900 mg garlic, 10 mg oil		−0.11* (−0.30, 0.08)	NR			NR	NR	NR	NR			8–24 wk	287	6 diet-controlled trials
900 mg, garlic 0.25 mg/kg bw oil		NR	NR			−0.17* (−0.35, 0.01)	NR	+0.07*	NR			12–24 wk	294	5 with additional lipid data
3–12 g psyllium[66]	6.39±0.09 (psyllium) 6.16±0.10	−0.31 (−0.37, −0.25)	−4.9*	NR	NR	−0.35 (−0.40, −0.29)	−8.1*	0.00 (−0.04, 0.03)	0*	−0.22*	−6.9*	14–56 d		12

NR=not reported; ( )=95% confidence interval; P=parallel; X=crossover; T=treatment; C=control, bw=body weight.
*Calculated from cited published data.
†Data in mM/g fiber multiplied by average daily fiber intake.
‡Nonsignificant.

A recent review[70] of three controlled clinical trials reported on 242 mildly hypercholesterolemic participants who consumed margarine or mayonnaise with stanol esters in daily amounts of 2 to 3.4 g. Total cholesterol concentrations fell by 15%, LDL by 20%. No obvious side effects have been noted with phytosterols, except in individuals with phytosterolemia, a rare inherited lipid disorder characterized by increased absorption and decreased biliary secretion of plant sterols and accelerated arteriosclerosis.[47]

Meta-analyses of soy, psyllium, oat, and garlic are compared in Table 7. The effects of soy products on total cholesterol lowering are comparable to those of garlic (soy 9%, garlic 9%–12%). Psyllium and oats produced values below these, although these results contrast with findings in other studies,[32,33] which reported extremely large changes.

The efficacy of garlic in improving lipid values is well accepted. Early meta-analyses of clinical trials of garlic unanimously demonstrated statistically significant benefits over placebo. More recently, however, several placebo-controlled trials[57,58,61,62,64] have failed to confirm garlic's lipid-lowering efficacy. This discrepancy may be rooted in methodologic differences such as the lack of diet protocols or well-defined diet control. Moreover, blinding may have been compromised in placebo-controlled trials, because many participants complained of altered body odor or garlic breath.[71] A meta-analysis[56] was conducted to consider the negative results of several recently published studies. Although plasma total cholesterol levels dropped significantly by 6%, no significant reduction was observed if only diet-controlled trials were analyzed. To date, a conclusive assessment of the lipid-lowering efficacy of garlic preparations is not possible. One report[71] pointed out that long-term studies of dosage and preparation types are required to confirm the efficacy of garlic in lowering cholesterol levels and to fully understand its potential role in cardiovascular disease.

The efficacy of the studies reviewed is illustrated by summaries of results with each natural product in terms of the LDL:HDL ratios (Table 8) and their mean (not weighted) effect (Table 9). All studies with Abacor and Abalon led to reproducible, statistically significant decreases in lipid parameters, especially LDL and total cholesterol and the LDL:HDL ratio. In all studies as well, a reliable increase in HDL cholesterol occurred with Abacor and Abalon, which stands in contrast to many other studies (eg, with plant sterols/stanol esters) in which HDL did not clearly change. HDL never decreased when Abacor or Abalon was added to the diet. ISP with standardized, fixed, high levels of isoflavones, soy fiber, and soy phospholipids positively affects blood cholesterol levels. The new products Abacor and Abalon therefore effectively reduce cardiovascular risk factors.

Table 8. Percent Decrease in LDL:HDL Ratio, All Studies

Study	Preparation	LDL:HDL Ratio, % Decrease	Study Duration, wk
Abacor and Abalon			
Tonstad et al[13]	Abacor 115 mg IF	22	16
Puska et al[11]	Abacor 192 mg IF	27	16
Abacor 397 CTR data	Abacor 192 mg IF	18	6
Hermansen et al[18]	Abacor 152 mg IF	7	8
	Abalon 165 mg IF	22	6
Soy products			
Wong et al[19]	Suprosoy	4–10	5
Baum et al[16]	ISP 56/ISP 90	10–14	24
Crouse et al[17]	Soy protein 62 mg IF	9	9
Washburn et al[18]	Soy protein 34 mg IF	1–3	6
Teixeira et al[15]	Supro Plus 675 HG	6	6
Merz-Demlow et al[20]	Soy protein 129 mg IF	3	8
Wangen et al[21]	Soy protein 65 mg IF	14	13
Kurowska et al[23]	Soy protein 132 mg IF	13	13
Ashton, Ball[22]	Soybean product	11	4
	Tofu	4	4
Psyllium			
Romero et al[33]	Psyllium	29–38	8
Rodriguez-Moran et al[32]	Psyllium	44	12
MacMahon, Carless[31]	Psyllium	11–12	12
Davidson et al[29]	Psyllium	4–5	24
Anderson et al[30]	Psyllium	3	26
Oats, Beta glucan			
Beer et al[38]	Beta glucan	–2	2
Pick et al[39]	Oat bran	29	12
Gerhardt, Gallo[34]	Oat bran	17	6
Behall et al[35]	Oat fiber	14–18	5
Önning et al[36]	Oat milk 3.8 g beta glucan	4	5
Lovegrove et al[37]	Oat bran	–6	12
Romero et al[33]	Oat bran	30–35	8
Plant stanols/sterols			
Miettinen et al[42]	Sitostanol	16	1 y
Miettinen et al[43]	Benecol	13	1
Blair et al[44]	Benecol	13	8
Hallikainen, Uusitupa[45]	Plant stanols	16–22	8
Hallikainen et al[46]	Plant stanols	7–11*	4
Gylling et al[47]	Sitostanol	13–14*	6
Denke[51]	Beta sitosterol	6*	3 mo
Westrate, Meijer[48]	Phytosterol (Take Control)	13*	3.5
Hendriks et al[52]	Benecol	12*	3.5
Jones et al[49]	Take Control	9*	3.5
	Sitostanol ester	10	3
Ayesh et al[53]	Beta-sitosterol ester	9	3
Jones et al[50]	Phytosterol mixture	13	3–4
	Phytrol/Reducol	15	4
Garlic preparations			
Neil et al[57]	Kwai garlic tablets	2	24
Simons et al[58]	Kwai garlic tablets	0.3	12
Gardner et al[61]	Garlic powder tablets	12	12
Superko et al[62]	Kwai garlic tablets	1	12
Lash et al[63]	Pure-Gar garlic tablets	1	44

IF=isoflavones; CTR=clinical trial report.
*Net changes.

Table 9. Summarized Effects of Various Natural Products*

		Abacor/ Abalon	Soy†	Psyllium‡	Oats/ Beta glucan‡	Plants Sterols/ Stanol Esters	Garlic
Total cholesterol, mM	Mean (initial)	6.82±0.77	5.82±1.02	6.27±0.67	5.86±1.08	5.99±0.58	6.38±0.88
	Mean (end)	6.08±0.76	5.54±1.03	5.70±0.67	5.26±0.85	5.33±0.57	6.34±0.51
	Range (initial)	5.68–7.53	3.64–6.78	5.43–6.98	3.74–7.21	4.88–6.73	4.47–7.50
	Range (end)	5.11–6.86	3.63–6.39	4.99–6.49	4.06–6.30	4.07–6.15	5.70–7.11
	% change (mean)	–10.9%	–4.8%	–9.1%	–6.8%	–5.7%	–0.6%
	No. of treatment groups	(n=5)	(n=11)	(n=7)	(n=9)	(n=18)	(n=7)
Triglycerides, mM	Mean (initial)	1.55±0.23	1.66±0.49	1.77±0.38	1.73±0.72	1.63±0.62	1.72±0.39
	Mean (end)	1.46±0.31	1.71±0.64	1.72±0.39	1.66±0.58	1.43±0.50	1.66±0.50
	Range (initial)	1.28–1.76	0.67–2.37	1.42–2.40	0.77–2.96	1.10–3.33	1.42–2.56
	Range (end)	0.59–1.64	0.69–3.00	1.43–2.39	0.84–2.78	1.05–3.00	1.24–2.39
	% change (mean)	–5.8%	+3.0%	–3.0%	–4.0%	–12.3%	–3.5%
	No. of treatment groups	(n=5)	(n=11)	(n=5)	(n=9)	(n=17)	(n=6)
LDL cholesterol, mM	Mean (initial)	4.65±0.61	4.04±1.01	4.38±0.61	3.95±0.83	3.95±0.60	4.58±0.33
	Mean (end)	3.95±0.67	3.73±0.95	3.83±0.59	3.37±0.70	3.42±0.58	4.39±0.42
	Range (initial)	3.63–5.13	2.15–5.22	3.65–5.07	2.49–5.09	2.53–4.54	4.19–4.99
	Range (end)	3.01–4.50	2.12–4.92	3.05–4.49	2.59–4.20	2.18–4.44	3.75–4.94
	% change (mean)	–15.0%	–7.7%	–12.6%	–14.7%	–13.4%	–4.1%
	No. of treatment groups	(n=5)	(n=11)	(n=7)	(n=9)	(n=18)	(n=16)
HDL cholesterol, mM	Mean (initial)	1.48±0.15	1.24±0.14	1.04±0.21	1.16±0.29	1.32±0.25	1.26±0.16
	Mean (end)	1.56±0.14	1.25±0.17	1.18±0.17	1.17±0.22	1.31±0.27	1.29±0.09
	Range (initial)	1.31–1.67	1.06–1.42	0.83–1.29	0.70–1.50	0.75–1.64	1.05–1.55
	Range (end)	1.38–1.67	0.96–1.42	0.93–1.32	0.83–1.40	0.67–1.63	1.17–1.47
	% change (mean)	+5.4%	+0.8%	+13.5%	+0.9%	+0.8%	+2.4%
	No. of treatment groups	(n=5)	(n=11)	(n=5)	(n=9)	(n=18)	(n=6)
LDL:HDL ratio	Mean (initial)	3.15±0.22	3.36±0.92	4.37±1.34	3.71±1.37	3.19±1.04	3.63±0.39
	Mean (end)	2.51±0.22	3.08±0.80	3.11±0.61	2.98±0.73	2.79±0.93	3.51±0.42
	Range (initial)	2.82–3.39	1.89–5.00	3.09–6.50	2.28–6.60	1.70–5.93	3.22–4.31
	Range (end)	1.38–1.67	1.83–4.50	2.31–4.00	2.32–4.65	1.48–5.03	3.12–4.22
	% change (mean)	–20.3%	–8.3%	–28.8%	–19.7%	–12.5%	–3.3%
	No. of treatment groups	(n=5)	(n=110)	(n=5)	(n=9)	(n=18)	(n=5)
No. of subjects, total		345	359	456	235	716	333
Dose/d		31–52 g ISP 115–192 mg isoflavones	20–85 g ISP 34–132 mg isoflavones	7–15 g psyllium	1.5–8.6 g phytosterol, 24–40 g margarine	3.2 g oat gum–100 g oat bran; 1.9–9 g beta glucan	900–7200 mg garlic powder/ extract

End=end of study.
*All means were calculated from means (not weighted).
†Only studies with ISP included.
‡Treatment groups with extremely high values included.

REFERENCES

1. Isles CG, Paterson JR. Identifying patients at risk for coronary heart disease: implications from trials of lipid-lowering drug therapy. *Q J Med.* 2000;93:567-574.
2. Stamler J, Daviglus ML, Garside DB, Dyer AR, Greenland P, Neaton JD. Relationship of baseline serum cholesterol levels in 3 large cohorts of younger men to long-term coronary, cardiovascular, and all-cause mortality and to longevity. *JAMA.* 2000;284:311-318.
3. American Heart Association. *2001 Heart and Stroke Statistical Update.* Dallas, Tex: American Heart Association; 2000:1-22.
4. Food and Drug Administration. Food labeling: health claims; oats and coronary heart disease; final rule (21 CFR part 101). *Federal Register.* January 23, 1997:3583-3601.
5. Food and Drug Administration. Food labeling: health claims; soluble fiber from certain foods and coronary heart disease; final rule (21 CFR part 101). *Federal Register.* February 18, 1998: 8103-8121.
6. Food and Drug Administration. Food labeling: health claims; plant sterol/stanol esters and coronary heart disease; interim final rule (21 CFR part 101). *Federal Register.* September 8, 2000: 54686-54739.
7. Food and Drug Administration. Food labeling: health claims; soy protein; interim final rule (21 CFR part 101.82). *Federal Register.* October 26, 1999:57700-57733.
8. Marsland C. A soy tutorial. *Nutritional World.* 2000;96-101.
9. Young VR. Soy protein in relation to human protein and amino acid nutrition. *J Am Diet Assoc.* 1991;91:828-835.
10. Anderson JW, Johnstone BM, Cook-Newell ME. Meta-analysis of the effects of soy protein intake on serum lipids. *N Engl J Med.* 1995;333:276-282.
11. Puska P, Korpelainen V, Hoie LH, Skovlund E, Lahti T, Smerud KT. Soy in hypercholesterolaemia: a double-blind, placebo-controlled trial. *Eur J Clin Nutr.* 2002;56:352-357.
12. Puska P, Korpelainen V, Hoie LH, Skovlund E, Smerud KT. Soy-fibre yogurt improves plasma lipids in hypercholesterolaemia: a double-blind, placebo-controlled trial. In press.
13. Tonstad S, Hoie L, Smerud KT. Effects of 2 doses of soy protein versus casein on serum lipids and lipoproteins and plasma total homocysteine in hypercholesterolemic subjects. *Am J Clin Nutr.* 2002;76:78-84.
14. Hermansen K, Sondergaard M, Hoie L, Carstensen M, Brock B. Beneficial effects of a soy-based dietary supplement on lipid levels and cardiovascular disease risk markers in type 2 diabetic subjects. *Diabetes Care.* 2001;24:228-233.
15. Teixeira SR, Potter SM, Weigel R, Hannum S, Erdman JW, Hasler CM. Effects of feeding 4 levels of soy protein for 3 and 6 wk on blood lipids and apolipoproteins in moderately hypercholesterolemic men. *Am J Clin Nutr.* 2000;71:1077-1084.
16. Baum JA, Teng H, Erdman JW, et al. Long-term intake of soy protein improves blood lipid profiles and increases mononuclear cell low-density-lipoprotein receptor messenger RNA in hypercholesterolemic, postmenopausal women. *Am J Clin Nutr.* 1998;68:545-551.
17. Crouse JR, Morgan T, Terry JG, Ellis J, Vitolins M, Burke GL. A randomized trial comparing the effect of casein with that of soy protein containing varying amounts of isoflavones on plasma concentrations of lipids and lipoproteins. *Arch Intern Med.* 1999;159:2070-2076.
18. Washburn S, Burke GL, Morgan T, Anthony M. Effect of soy protein supplementation on serum lipoproteins, blood pressure, and menopausal symptoms in perimenopausal women. *Menopause.* 1999;6:7-13.
19. Wong WW, Smith EO, Stuff JE, Hachey DL, Heird WC, Pownell HJ. Cholesterol-lowering effect of soy protein in normocholesterolemic and hypercholesterolemic men. *Am J Clin Nutr.* 1998;68: 1385S-1389S.

20. Merz-Demlow BE, Duncan AM, Wangen KE, et al. Soy isoflavones improve plasma lipids in normocholesterolemic, premenopausal women. *Am J Clin Nutr.* 2000;71:1462-1469.

21. Wangen KE, Duncan AM, Xu X, Kurzer MS. Soy isoflavones improve plasma lipids in normocholesterolemic and mildly hypercholesterolemic postmenopausal women. *Am J Clin Nutr.* 2001;73: 225-231.

22. Ashton E, Ball M. Effects of soy as tofu vs meat on lipoprotein concentrations. *Eur J Clin Nutr.* 2000;54:14-19.

23. Kurowska EM, Jordan J, Spence JD, et al. Effects of substituting dietary soybean protein and oil for milk protein and fat in subjects with hypercholesterolemia. *Clin Invest Med.* 1997;20:162-170.

24. Brown L, Rosner B, Willet WW, Sacks FM. Cholesterol-lowering effects of dietary fiber: a meta-analysis. *Am J Clin Nutr.* 1999;69:30-42.

25. Nordgaard I, Hove H, Clausen MR, Mortensen PB. Colonic production of butyrate in patients with previous colonic cancer during long-term treatment with dietary fibre (*Plantago ovata* seeds). *Scand J Gastroenterol.* 1996;31:1011-1020.

26. Lia A, Andersson H, Mekki N, Juhel C, Senft M, Lairon D. Postprandial lipemia in relation to sterol and fat excretion in ileostomy subjects given oat-bran and wheat test meals. *Am J Clin Nutr.* 1997;66:357-365.

27. Hendler SS, Rorvik MS, Fleming T, Deutsch M, Wyble C, eds. Psyllium. In: *PDR® for Nutritional Supplements.* Montvale, NJ: Thomson Healthcare; 2001:384-386.

28. Anderson JW, Allgood LD, Lawrence A, Altringer LA, Jerdack GR, Hengehold DA. Cholesterol-lowering effects of psyllium intake adjunctive to diet therapy in men and women with hypercholesterolemia: meta-analysis of 8 controlled trials. *Am J Clin Nutr.* 2000;71:472-479.

29. Davidson MH, Maki KC, Kong JC, et al. Long-term effects of consuming foods containing psyllium seed husk on serum lipids in subjects with hypercholesterolemia. *Am J Clin Nutr.* 1998;67:367-376.

30. Anderson JW, Davidson MH, Blonde L, et al. Long-term cholesterol-lowering effects of psyllium as an adjunct to diet therapy in the treatment of hypercholesterolemia. *Am J Clin Nutr.* 2000;71: 1433-1438.

31. MacMahon M, Carless J. Ispaghula husk in the treatment of hypercholesterolaemia: a double-blind controlled study. *J Cardiovasc Risk.* 1998;5:167-172.

32. Rodriguez-Morán M, Guerrero-Romero F, Lazcano-Burciaga G. Lipid- and glucose-lowering efficacy of plantago psyllium in type II diabetes. *J Diabetes Complications.* 1998;12:273-278.

33. Romero AL, Romero JE, Galaviz S, Fernandez ML. Cookies enriched with psyllium or oat bran lower plasma LDL cholesterol in normal and hypercholesterolemic men from northern Mexico. *J Am Coll Nutr.* 1998;17:601-608.

34. Gerhardt AL, Gallo NB. Full-fat rice bran and oat bran similarly reduce hypercholesterolemia in humans. *J Nutr.* 1998;128:865-869.

35. Behall KM, Scholfield DJ, Hallfrisch J. Effect of beta-glucan level in oat fiber extracts on blood lipids in men and women. *J Am Coll Nutr.* 1997;16:46-51.

36. Önning G, Wallmark A, Persson M, Akesson B, Elmstahl S, Öste R. Consumption of oat milk for 5 weeks lowers serum cholesterol and LDL cholesterol in free-living men with moderate hypercholesterolemia. *Ann Nutr Metab.* 1999;43:301-309.

37. Lovegrove JA, Clohessy A, Milon H, Williams CM. Modest doses of β-glucan do not reduce concentrations of potentially atherogenic lipoproteins. *Am J Clin Nutr.* 2000;72:49-55.

38. Beer MU, Arrigoni E, Amadò R. Effects of oat gum on blood cholesterol levels in healthy young men. *Eur J Clin Nutr.* 1995;49:517-522.

39. Pick ME, Hawrysh ZJ, Gee MI, Toth E, Garg ML, Hardin RT. Oat bran concentrate bread products improve long-term control of diabetes: a pilot study. *J Am Diet Assoc.* 1996;96:1254-1261.

40. Plat J, Mensink RP. Vegetable oil based versus wood based stanol ester mixtures: effects on serum lipids and hemostatic factors in non-hypercholesterolemic subjects. *Atherosclerosis.* 2000; 148:101-112.

41. Ling WH, Jones PJH. Minireview. Dietary phytosterols: a review of metabolism, benefits and side effects. *Life Sci.* 1995;57:195-206.

42. Miettinen TA, Puska P, Gylling H, Vanhanen H, Vartiainen E. Reduction of serum cholesterol with sitostanol-ester margarine in a mildly hypercholesterolemic population. *N Engl J Med.* 1995;333:1308-1312.

43. Miettinen TA, Vuoristo M, Nissinen M, Järvinen HJ, Gylling H. Serum, biliary, and fecal cholesterol and plant sterols in colectomized patients before and during consumption of stanol ester margarine. *Am J Clin Nutr.* 2000;71:1095-1102.

44. Blair SN, Capuzzi DM, Gottlieb SO, Nguyen T, Morgan JM, Cater NB. Incremental reduction of serum total cholesterol and low-density lipoprotein cholesterol with the addition of plant stanol ester-containing spread to statin therapy. *Am J Cardiol.* 2000;86:46-52.

45. Hallikainen MA, Uusitupa MIJ. 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;69:403-410.

46. Hallikainen MA, Sarkkinen ES, Uusitupa MIJ. Plant stanol esters affect serum cholesterol concentrations of hypercholesterolemic men and women in a dose-dependent manner. *J Nutr.* 2000;130:767-776.

47. Gylling H, Miettinen TA. Cholesterol reduction by different plant stanol mixtures and with variable fat intake. *Metabolism.* 1999;48:575-580.

48. Weststrate JA, Meijer GW. Plant sterol-enriched margarines and reduction of plasma total- and LDL-cholesterol concentrations in normocholesterolaemic and mildly hypercholesterolaemic subjects. *Eur J Clin Nutr.* 1998;52:334-343.

49. Jones PJ, Raeini-Sarjaz M, Ntanios FY, Vanstone CA, Feng JY, Parsons WE. Modulation of plasma lipid levels and cholesterol kinetics by phytosterol versus phytostanol esters. *J Lipid Res.* 2000;41: 697-705.

50. Jones PJH, Ntanios FY, Raeini-Sarjaz M, Vanstone CA. Cholesterol-lowering efficacy of a sitostanol-containing phytosterol mixture with a prudent diet in hyperlipidemic men. *Am J Clin Nutr.* 1999; 69:1144-1150.

51. Denke MA. Lack of efficacy of low-dose sitostanol therapy as an adjunct to a cholesterol-lowering diet in men with moderate hypercholesterolemia. *Am J Clin Nutr.* 1995;61:392-396.

52. Hendriks HFJ, Weststrate JA, van Vliet T, Meijer GW. Spreads enriched with three different levels of vegetable oil sterols and the degree of cholesterol lowering in normocholesterolaemic and mildly hypercholesterolaemic subjects. *Eur J Clin Nutr.* 1999;53:319-327.

53. Ayesh R, Weststrate A, Drewitt PN, Hepburn PA. Safety evaluation of phytosterol esters, Part 5: faecal short-chain fatty acid and microflora content, faecal bacterial enzyme activity and serum female sex hormones in healthy normolipidaemic volunteers consuming a controlled diet either with or without a phytosterol ester-enriched margarine. *Food Chem Toxicol.* 1999;37:1127-1138.

54. Silagy C, Neil A. Garlic as a lipid lowering agent—a meta-analysis. *J R Coll Physicians Lond.* 1994; 28:2-8.

55. Warshafsky S, Kamer RS, Sivak SL. Effect of garlic on total serum cholesterol. *Ann Intern Med.* 1993;119:599-605.

56. Stevinson C, Pittler MH, Ernst E. Garlic for treating hypercholesterolemia. A meta-analysis of randomized clinical trials. *Ann Intern Med.* 2000;133:420-429.

57. Neil HAW, Silagy CA, Lancaster T, et al. Garlic powder in the treatment of moderate hyperlipidaemia: a controlled trial and meta-analysis. *J R Coll Physicians Lond.* 1996;30:329-334.

58. Simons LA, Balasubramaniam S, Königsmark M, Parfitt A, Simons J, Peters W. On the effect of garlic on plasma lipids and lipoproteins in mild hypercholesterolaemia. *Atherosclerosis.* 1995; 113:219-225.

59. Bordia A, Verma SK, Srivastava KC. Effect of garlic *(Allium sativum)* on blood lipids, blood sugar, fibrinogen and fibrinolytic activity in patients with coronary artery disease. *Prostaglandins, Leukot Essent Fatty Acids.* 1998;58:257-263.

60. Yeh YY, Liu L. Cholesterol-lowering effect of garlic extracts and organosulfur compounds: human and animal studies. *J Nutr.* 2001;131:989S-993S.

61. Gardner CD, Chatterjee LM, Carlson JJ. The effect of a garlic preparation on plasma lipid levels in moderately hypercholesterolemic adults. *Atherosclerosis.* 2001;154:213-220.

62. Superko HR, Krauss RM. Garlic powder: effect on plasma lipids, postprandial lipemia, low-density lipoprotein particle size, high-density lipoprotein subclass distribution and lipoprotein (a). *J Am Coll Cardiol.* 2000;35:321-326.

63. Lash JP, Cardoso LR, Mesler PM, Walczak DA, Pollak R. The effect of garlic on hypercholesterolemia in renal transplant patients. *Transplant Proc.* 1998;30:189-191.

64. Isaacsohn JL, Moser M, Stein EA, et al. Garlic powder and plasma lipids and lipoproteins. A multicenter, randomized, placebo-controlled trial. *Arch Intern Med.* 1998;158:1189-1194.

65. Hendler SS, Rorvik MS, Fleming T, Deutsch M, Wyble C, eds. Soy isoflavones, soy proteins. In: *PDR® for Nutritional Supplements.* Montvale, NJ: Thomson Healthcare; 2001:428-431.

66. Olson BH, Anderson SM, Becker MP, et al. Psyllium-enriched cereals lower blood total cholesterol and LDL cholesterol, but not HDL cholesterol, in hypercholesterolemic adults: results of a meta-analysis. *J Nutr.* 1997;127:1973-1980.

67. Wood PJ, Beer MU. Functional oat products. In: Mazza G, ed. *Functional Foods.* Basel: Technomic; 1998:1-37.

68. Lo GS, Goldberg AP, Lim A, Grundhauser JJ, Anderson C, Schonfeld G. Soy fiber improves lipid and carbohydrate metabolism in primary hyperlipidemic subjects. *Atherosclerosis.* 1986;62:239-248.

69. Anderson JW, Deakins DA, Floore TL, Smith BM, Whitis SE. Dietary fiber and coronary heart disease. *Crit Rev Food Sci Nutr.* 1990;29:95-147.

70. Miettinen TA. Stanol esters in treatment of hypercholesterolaemia. *Eur Heart J Suppl.* 1999; 1(suppl S):S50-S57.

71. Spigelski D, Jones PJH. Efficacy of garlic supplementation in lowering serum cholesterol levels. *Nutr Rev.* 2001;59:236-244.

ISSN: 0741-238X

Advances In Therapy®

The International Journal of Drug, Device & Diagnostic Research

January/February 2003 *Volume 20 No. 1*

CONTENTS

Advances In Natural Therapy™

HCI Health Communications Inc