Appendix 8 - Plant Sterols Clinical Trials

The literature search strategy used were MEDLINE and-EMBASE databases which were searched for publications dating from January 2012 to 15 December 2015. Articles were identified using the key word phytosterols, phytostanols, plant sterols and plant stanols. Further, the articles were then selected based on the peer reviewed type and clinical trials. 67 journals were generated and examined and 29 were selected for review.

Studies were excluded using the following reasons:

1. Not related to plant sterols
2. Combination therapies with other nutraceuticals or drugs
3. Not written in English
4. Subjects only given food naturally containing plant sterols
5. Duplicates
6. Reviewed journals

All 29 selected studies conducted on human subjects reported no adverse events attributable to the consumption of plant sterols or stanols (Table1). This finding is consistent with a 2014 report by a European Atherosclerosis panel, published in Atherosclerosis, which concluded that no harm is to be anticipated by the intake of plant sterol and stanol containing foods (Gylling et al., 2014). This panel also concluded that concerns raised by some researchers were not supported by conclusive evidence.
Furthermore, a recent review (Silbernagel et al. 2015) **has** summarised and re-evaluated the four most important arguments against the use of plant sterol and stanol containing functional foods and concluded that there is no evidence that consumption of plant sterol and stanol containing functional foods may cause harm to consumers.

Table 1: Human studies with phytosterols

Type of study (reference)	Subject details	Treatment details (dose, duration, route)	Adverse reactions and safety indicators	Endpoints	Key outcomes
A randomized, double blind, cross-over study (Baumgartner, Mensink, Husche, Lutjohann, & Plat, 2013)	43 healthy subjects (18-70 years)	4 weeks treatment with a plant sterol-enriched (3.0 g/d of plant sterols), a plant stanol-enriched (3.0 g/d of plant stanols), and a control margarine separated by wash-out periods of 4 weeks	No Reported adverse events	Plasma oxyphytosterol concentrations serum LDL-C concentrations	Compared to control, serum LDL-C concentrations were reduced after plant sterol (-8.1%; $p < 0.001$) and plant stanol consumption (-7.8%; $p < 0.001$). Plant sterol consumption did not change plasma oxyphytosterol concentrations. The plant stanol margarine reduced 7b-OH-campesterol by 0.07 ng/mL (w14%; $p < 0.01$) and by 0.07 ng/mL (w15%; $p < 0.01$) compared with the control and sterol margarines, respectively.
An open-label Intervention trial	Thirty-five individuals (88.6% women; 81 ± 8 years old; BMI	Daily intake of 2 g low-fat phytostanol enriched fermented milk for 6 weeks, in	No Reported adverse events	A fasting blood sample was collected at baseline (t0), after 2 consecutive	PS-FM consumption led to a LDL-C reduction of 0.15 mmol/L (t1) and 0.27 mmol/L (t2) from baseline ($P < 0.05$). Serum campesterol and sitosterol

Type of study (reference)	Subject details	Treatment details (dose, duration, route)	Adverse reactions and safety indicators	Endpoints	Key outcomes
(Andrade, Santos, & Ramos, 2015)	29.9 ± 6.0 kg/m2), Statin-treated elderly individuals, with baseline LDL-C < 3.35 mmol/L,	addition to statin monotherapy.		periods of 3 weeks intake (t1 and t2), and after 6 weeks of washout (t3), for the analysis of serum lipid profile and cholesterol synthesis (lathosterol, desmosterol) and absorption (sitosterol, campesterol and cholestanol) markers	(P < 0.001) increased (t0–t1; t0–t2), reflecting PS intake and contributing to the inhibition of cholesterol intestinal absorption, leading to a decrease in cholestanol-to-cholesterol ratio.
A randomized, double-blinded, placebo-controlled. (Becker, French, Morris, Silvent, & Gordon, 2013)	A total of 187 participants (mean low-density lipoprotein cholesterol [LDL-C], 154 mg/dL)	Red yeast rice (RYR) 1800 mg twice daily and were randomised to phytosterol tablets 900 mg twice daily or placebo.	Four participants experienced intractable myalgias however all had a history of statin-associated myalgias. Another participant's supplements were discontinued at week 12 because of transaminases 3× the upper limit of normal. No elevations of CPK in any group. 3 participants in the placebo group stopped supplements, 1 because of a rash attributed to RYR and 2 because of gastrointestinal adverse effects	Change in LDL-C at 12, 24, and 52 weeks. Secondary end points were effect on other lipoproteins, high-sensitivity C-reactive protein, weight, and development of myalgia.	Phytosterols did not significantly improve LDL-C at weeks 12 (P = .54), 24 (P = .67), or 52 (P = .76) compared with placebo.
A randomised, double-blind, placebo-	Seventy subjects with untreated mild to moderate	115 g low-fat yoghurt with 1.9 g/d plant stanols as esters or	No adverse effects reported.	Changes in the lipid profile, including lipoproteins,	Serum total cholesterol (4.6%), LDL cholesterol (6.3%), and non-HDL cholesterol (6.2%)

Type of study (reference)	Subject details	Treatment details (dose, duration, route)	Adverse reactions and safety indicators	Endpoints	Key outcomes
controlled study. (Buyuktuncer, Fisunoglu, Guven, Unal, & Besler, 2013)	hypercholesterolemia (aged 23-65 years)	placebo yoghurt for 4 weeks.		apolipoproteins, and triglycerides, and anthropometric measurements .	concentrations were reduced significantly from baseline in the plant stanol group compared to the control group ($p = 0.007$, $p = 0.005$ and $p = 0.005$, respectively). No significant change in anthropometrical measurements was observed.
A randomised, placebo-controlled, crossover study (Casas-Agustench et al., 2012)	43 subjects with LDL-C . 1300 mg/l	500ml of skimmed milk with 2g phytosterols (PS-SM) or semi-enriched with vegetable fat (PS-VFM) with 2g of phytosterols. Control 200ml of skimmed milk with no phytosterols	No adverse effects reported.	Serum concentrations of lipids and non-cholesterol sterols	Consumption of 2 g/d of phytosterols as PS-SM and PS-VFM lowered LDL-C in hypercholesterolaemic subjects to a similar extent. Basal and post-treatment changes in markers of cholesterol metabolism indicating low cholesterol synthesis and high cholesterol absorption predicted improved LDL-C responses to PS.
Intervention study (Feuerstein & Bjerke, 2012)	18 patients with hypercholesterolemia	Supplement containing 1,200 mg of red yeast rice and 1,250 mg of phytosterol	None of the participants in the study reported any muscle pains, and no abnormal liver function tests were seen while taking the product	Blood lipids	Statistically significant reduction ($p < .05$) in the following mean variables was seen: total cholesterol 19%(46 mg/dL) and LDL 33% (53 mg/dL) after 6 weeks using the blend. There was no significant difference in body mass index (BMI), triglyceride, high-density lipoprotein (HDL) cholesterol levels, or systolic and diastolic blood pressure over the same period.
An open-label two years' prospective study. (Garoufi et al., 2014)	59 children, 25 with LDL-C ≥ 3.4 mmol/l (130 mg/dl) and 34 with LDL-C < 3.4 mmol/l, aged 4.5-15.9 years,	A yogurt-drink enriched with 2 g of plant sterols.	No adverse effects reported.	Blood lipids	The consumption of plant sterols reduced sdLDL-C significantly ($p < 0.001$). TC, LDL-C, HDL-C and apolipoprotein B (ApoB) levels also decreased significantly ($p < 0.05$). The median reduction of sdLDL-C and LDL-C was 16.6% and 13%, respectively..

Appendix 8: Safety – Plant Sterol Clinical Trials / Literature Search

Type of study (reference)	Subject details	Treatment details (dose, duration, route)	Adverse reactions and safety indicators	Endpoints	Key outcomes
A randomized, double-blind, crossover study. (Granado-Lorencio et al., 2014)	38 postmenopausal women	b-cryptoxanthin b-Cx (0.75 mg/day) and phytosterols (1.5 g/day), single and combined. b-Cx and phytosterol were supplemented with 1 - 250 mL milk-based fruit drink/day for 4 weeks with a wash-out period of 4- weeks in between	No adverse effects reported.	Outcome variables included markers of bone turnover and cardiovascular risk.	The beverage containing b-Cx plus phytosterol brought about significant decreases in total cholesterol, c- HDL, c-LDL and bone turnover markers.
A randomized, controlled, double-blind, parallel trial and lasted 6 months. (Gylling et al., 2013)	92 asymptomatic subjects, 35 men and 57 women, mean age of 50.8±1.0 years (SEM)	The staest group (n=46) consumed rapeseed oil-based spread enriched with staest (3.0 g of plant stanols/d), and controls (n=46) the same spread without staest	No adverse effects reported.	Arterial stiffness was assessed via the cardio-ankle vascular index (CAVI) in large and as an augmentation index (AI) in peripheral arteries, and endothelial function as reactive hyperemia index (RHI). Lipids and vascular endpoints were tested	Lowering LDL and non-HDL cholesterol by 10% with staest for 6 months reduced arterial stiffness in small arteries. In subgroup analyses, staest also had a beneficial effect on arterial stiffness in large arteries in men and on endothelial function
A randomised, double-blind, placebo-controlled study. (Hautaniemi et al., 2015)	104 subjects with the metabolic syndrome (MetS)	3 groups received a fermented milk product containing (1) 5 mg/d lactotripeptides (LTP) and 2 g/d plant sterols (PS); (2) 25 mg/d LTP and 2 g/d PS; (3) placebo for 12 weeks.	No adverse effects reported.	Plasma lipids and home BP were monitored.	No antihypertensive effect of LTP and PS intake in fermented milk product at home or in the laboratory, but a mild lipid-lowering effect in subjects with the MetS.
A double-blinded, randomized, crossover trial.	58 hypercholesterolemic subjects	the two sterol margarines (2g per day) and a control non-sterol	No adverse effects reported.	Concentrations of vascular cell adhesion molecule-l	Rapeseed-sterol margarine reduced E-selectin concentrations compared to the control

Type of study (reference)	Subject details	Treatment details (dose, duration, route)	Adverse reactions and safety indicators	Endpoints	Key outcomes
(Heggen, Kirkhus, Pedersen, & Tonstad, 2015)		margarine for 4 weeks separated by one-week washout periods		(VCAM-1), E-selectin, circulating tumour necrosis factor α (TNF α) and plasminogen activator inhibitor-1 (total, tPAI-1; active, PAI-1)	margarine (p =0.012) while tall-sterol margarine had no effect. The Rapeseed-sterol margarine reduced tPAI-1 (p =0.008) compared to the tall-sterol margarine. No significant changes were observed in TNF α and VCAM-1. No association was found between LDL reduction and changes in E-selectin and tPAI-1.
Randomised single blinded Study (Hongu et al., 2014)	24 overweight and obese adults (age: 43 ± 6 years, body mass index 32 ± 1 kg/m2, 18 females)	A group of were randomized to a 25% calorie-restricted diet containing either pigmented rice bran (RB) or the RB with addition of plant sterols (RB + PS) snack bars for 8 weeks Total sterol levels were 1.8 g per day	No adverse effects reported.	Anthropometrics, blood pressure, blood lipids, glucose, urinary F2-isoprostanes, C-reactive protein, insulin, and leptin were measured at baseline and after 8 weeks of intervention.	A nutrient-balanced and energy-restricted diet supplemented with rice bran and plant sterols resulted in a significant decrease in total and LDL cholesterol in overweight and obese adults.
An open-label intervention study (Keller et al., 2013)	14 women	Dairy products enriched with moderate (3 g PL/ day) or high (6 g PL/day) dose of milk PL or a high dose of milk PL combined with PSt (6 g PL/day + 2 g PSt/day) during 3 periods each lasting 10 days	No adverse effects reported.	Blood lipids	Milk PL supplementations influence plasma cholesterol concentrations, but without changes of LDL/HDL ratio. A combined high-dose milk PL and PSt supplementation decreases plasma LDL cholesterol concentration.
A randomized, single-centre, controlled study with crossover design. (Keszthelyi et al., 2013)	12 healthy male volunteers	Three treatments were tested; a 100 mL PS yoghurt drink (labelled with 1,000 mg acetaminophen) was consumed 45 min prior to, during and 45 min after a solid meal	No adverse effects reported.	Plasma samples were taken, and gallbladder volumes were measured at baseline and at regular intervals during a 6-h study period.	When consumed before the consumption of a meal, the yoghurt drink exhibited fast gastric emptying. The solid meal intake caused a significant contraction of the gallbladder. Consumption of the PS drink before the meal had no significant effect on gallbladder volume as

Type of study (reference)	Subject details	Treatment details (dose, duration, route)	Adverse reactions and safety indicators	Endpoints	Key outcomes
					compared to baseline and compared to during and after meal consumption.
Double-blinded randomized controlled trial study. (Kietsiriroje, Kwankaew, Kitpakornsanti, & Leelawattana, 2015)	240 subjects with a baseline LDL-c of 130 mg/dl or higher.	2 g/day of phytosterols and 10 g/day of inulin-enriched soymilk or the control group with the consumption of standard soymilk only for 8 weeks	Study concluded that both soymilk products were comparably safe	Blood lipids	Daily consumption of soymilk containing 2 g of phytosterols and 10 g of inulin reduced TC and LDL-c better than standard soymilk. It had no effect on TG and HDL-c levels compared to standard soymilk. .
A dual-center, single-blind, randomized crossover design. (Mackay, Gebauer, Eck, Baer, & Jones, 2015)	63 mildly hypercholesterolemic adults who were preselected as possessing either high endogenous cholesterol synthesis [HS; n = 24; L:C = 2.03 6 0.39 mmol/mmol (mean 6 SD)] or low endogenous cholesterol synthesis (LS; n = 39; L:C = 0.99 6 0.28 mmol/mmol) on the basis of baseline L:C	Consumed 2 g phytosterol (PS) per day or a placebo for 28 d	No adverse effects reported.	Plasma lipids and non-cholesterol sterol concentrations	PS consumption lowered total cholesterol and LDL cholesterol. Specifically, LS individuals responded to PS treatment with a reduction in TC (20.40 6 0.07 mmol/L; P , 0.0001) and LDL cholesterol (20.29 6 0.05 mmol/L; P = 0.0002), whereas HS individuals failed to show cholesterol lowering (TC: 20.09 6 0.09 mmol/L; P = 0.2843; LDL cholesterol: 20.05 6 0.07 mmol/L; P = 0.4917). The L:C ratio predicts the extent of reduction in circulating TC and LDL cholesterol in response to PS consumed.
This randomized, placebo-controlled, crossover (Maki et al., 2013). Results confirmed independently by McKenney et al. (2014)	28 participants with primary hypercholesterolemia (LDL-C levels 130 and <220 mg/dL)	Soft gel dietary supplement, providing esterified plant sterols/stanols 1.8 g/d	No adverse effects reported.	Blood lipids	The mean baseline lipid concentrations (mg/dL) were 223 for total cholesterol (TC), 179 for non–high-density lipoprotein cholesterol (non-HDL-C), 154 for low density lipoprotein cholesterol, 44 for HDL-C, 125 for triacylglycerols, and 5.2 for TC/HDL-C. Differences from the control responses (plant sterol/stanol minus control) in the per-

Type of study (reference)	Subject details	Treatment details (dose, duration, route)	Adverse reactions and safety indicators	Endpoints	Key outcomes
					protocol sample were significant (P < 0.05) for LDL-C, non-HDL-C , TC , TC/HDL-C and triacylglycerols. The HDL-C responses were not significantly different between treatments.
A prospective, randomized, open-label study, with parallel arms and blinded end points (Malina et al., 2015)	86 subjects	Subjects received atorvastatin 40 mg, ezetimibe 10 mg, or combination of both drugs for another 4-wk period (phase I). In phase II, capsules containing 2.0 g of phytosterols were added to previous assigned treatments for 4 weeks	No adverse effects reported.	Blood lipids, apolipoproteins, plasma campesterol, b-sitosterol, and desmosterol.	Compared with baseline, atorvastatin 40 mg reduced total and LDL cholesterol (3% and 22%, respectively, P <0.05), increased b-sitosterol, campesterol/cholesterol, and b-sitosterol/cholesterol ratios (39%, 47%, and 32%, respectively, P<0.05); ezetimibe 10 mg reduced campesterol and campesterol/cholesterol ratio (67% and 70%, respectively, P , .05), and the combined therapy decreased total and LDL cholesterol (22% and 38%, respectively, P <0.05), campesterol, b-sitosterol, and campesterol/cholesterol ratio (54%, 40%, and 27%, P ,.05). Addition of PS further reduced total and LDL cholesterol by w7.7 and 6.5%, respectively, in the atorvastatin therapy group and 5.0 and 4.0% in the combined therapy group (P ,.05, for all), with no further effects in absorption or synthesis markers.
A double-blind, randomized, crossover, placebo-controlled study. (Myrie, Mymin, Triggs-Raine, & Jones, 2012)	10 phytosterolemia heterozygotes (HET) adults and 15 healthy control subjects.	1.6 g phytosterol or placebo capsules daily for 4 weeks	No adverse effects reported.	Blood lipids and phytosterols	Plasma LDL-cholesterol concentrations decreased (P = 0.006) in both groups after PS supplementation compared with placebo, whereas PS concentrations (campesterol+b-sitosterol) increased (P = 0.03)

Type of study (reference)	Subject details	Treatment details (dose, duration, route)	Adverse reactions and safety indicators	Endpoints	Key outcomes
					in both groups after PS supplementation compared with placebo. Cholesterol absorption efficiency decreased (P = 0.010) by 22% and 17% and synthesis rates increased (P = 0.040) by 20% and 24% in the HET and control groups, respectively, in response to PS consumption compared with placebo.
In a double-blinded, randomized, placebo-controlled crossover study. (Ottestad et al., 2013)	41 subjects	Softgel capsules containing either phytosterols (2.0 g/d) or sunflower oil as control for 4 weeks.	No adverse effects reported.	Blood lipids	No significant difference in total or LDL-cholesterol between the phytosterol and the placebo period were observed after four weeks intervention (0.0 mmol/L (95%CI: 0.3 to 0.2), P = 0.74 and 0.1 mmol/L (95%CI: 0.3 to 0.1), P = 0.32, respectively).
A two-arm longitudinal crossover. (Padro et al., 2015)	32 overweight and moderately hypercholesterolemic subjects	Milk (250 ml/day), enriched with either 1.57 g phytosterols (PS)or 375 mg omega 3 (EPA + DHA), for 28 days	No adverse effects reported.	Blood lipids	Compared with baseline, PS-milk induced a higher reduction in the LDL cholesterol (LDLc) level than omega 3-milk. LDL resistance to oxidation was significantly increased after intervention with PS-milk. Changes in TGL and VLDL cholesterol were only evident after _ 3-milk intake. Lipidomic analysis revealed a differential effect of the PS- and omega 3-milk interventions on the LDL lipid metabolite pattern. Content in LDL-glycerophospholipids was reduced after PS milk intake.
In a double-blinded, randomized, placebo-controlled.	101 Hypercholesterolaemic subjects aged 40–60 years.	Low-fat milk that was enriched with phytosterols, a-linolenic and linoleic fatty acids, vitamins and antioxidants	No adverse effects reported.	Anthropometric measurements, blood pressure, 24h food recall, physical activity and blood biochemistry.	Regarding lifestyle changes, total and saturated fat intakes decreased significantly in both intervention groups compared with the CG (P <0.005).

Type of study (reference)	Subject details	Treatment details (dose, duration, route)	Adverse reactions and safety indicators	Endpoints	Key outcomes
(Petrogianni et al., 2014)		(enriched milk group, EMG, a placebo milk group (PMG) or a control group (CG). The EMG and PMG consumed respectively 500 ml of enriched milk or placebo milk daily and attended biweekly counselling sessions over a 3-month period.			Furthermore, total steps were increased (P = 0.029) and BMI was decreased (P = 0.017) significantly in both intervention groups compared with the CG. Regarding biochemical indices, EPA content in erythrocyte membranes increased (P < 0.001) while serum C-reactive protein decreased (P = 0.003) significantly in both intervention groups compared with the CG. Significant increases in plasma folic acid and vitamin B12 levels and a significant decrease in homocysteine levels were observed in the EMG compared with the PMG and CG (all P <0.001). A favourable change in LDL cholesterol:HDL cholesterol was also observed in the EMG and tended to be significant compared with the PMG and CG (P =0.066)
A randomized, double-blind, placebo controlled parallel study. (Ras et al., 2014)	85 hypercholesterolemic men and 247 women with a mean age of 57.9 y (range: 25–74 y)	Subjects were randomly assigned to consume either a control (C) spread (no PSs, no FO) or 1 of 4 intervention spreads containing a fixed amount of PSs (2.5 g/d) and varying amounts of FO (0.0, 0.9, 1.3, and 1.8 g/d of EPA+DHA) for 4 wk.	No adverse effects reported.	Serum lipids and EPA and DHA in erythrocyte membranes	Baseline, mean TG and LDL-C concentrations were 1.09 and 4.00 mmol/L, respectively. After the intervention, a significant dose-response relation for the TG-lowering effect of EPA +DHA [bln(TG) =20.07 mmol/L per gram of EPA+DHA; P < 0.01] was found. Compared with the C group, TG concentrations were 9.3–16.2% lower in the different FO groups (P < 0.05 for all groups). LDL-C concentrations were 11.5–14.7% lower in the different PS groups than in the C group (P < 0.01 for all groups). EPA and DHA in erythrocyte membranes were dose-dependently higher after FO intake

Type of study (reference)	Subject details	Treatment details (dose, duration, route)	Adverse reactions and safety indicators	Endpoints	Key outcomes
					than after the C spread, indicating good compliance. Consumption of a low-fat spread enriched with PSs and different low doses of n–3 fatty acids from FO decreased TG concentrations in a dose-dependent manner and decreased LDL-C concentrations
A double-blind, randomized, placebo-controlled, parallel design. (Ras et al., 2015)	240 hypercholesterolemic but otherwise healthy men and women	Consumed 20 g/d of low-fat spread without (control) or with added PSs (3 g/d) during 12 weeks.	No adverse effects reported.	Pre and Post intervention, vascular function measurements and blood sampling were performed.	PS intake did not affect FMD (+0.01 percentage points; 95% CI: 20.73, 0.75) compared with control. Measures of arterial stiffness (pulse wave velocity and augmentation index) and blood pressure were also not significantly changed compared with control. After PS intervention, LDL cholesterol significantly decreased on average by 0.26 mmol/L (95% CI: 20.40, 20.12) or 6.7% compared with control. Plasma sitosterol and campesterol concentrations significantly increased in the PS group up to on average 11.5 mmol/L and 13.9 mmol/L (expressed as geometric means), respectively.
In a parallel arm, randomized placebo-controlled design. (Sialvera et al., 2013)	108 patients with metabolic syndrome	Subjects consumed yogurt beverage which provided 4 g of phytosterols per day or yogurt beverage without phytosterols. The duration of the study was 2 months	No adverse effects reported.	the total antioxidant capacity of plasma oxygen radical absorbance capacity assays	Plasma total antioxidant capacity did not differ between and within the intervention and the control groups.
A controlled, randomized, double-blind study.	92 normo- to moderately hypercholestero	consumed vegetable-oil spread	No adverse effects reported.	Serum PCSK9, Lipids and sterols	At baseline, PCSK9 concentration varied from 91 to 716 ng/ml with a mean value of 278+−11

Type of study (reference)	Subject details	Treatment details (dose, duration, route)	Adverse reactions and safety indicators	Endpoints	Key outcomes
(Simonen, Stenman, & Gylling, 2015)	laemic subjects (35 males and 57 females)	20 g/day enriched (plant stanol group, *n*=46) or not (control group, *n*=46) with plant stanols 3 g/day as ester for 6 months			(S.E.M.) ng/ml with no gender difference. It correlated with serum and LDL-C, serum triglycerides, age, body mass index (BMI) and plasma glucose concentration, but not with variables of cholesterol metabolism when adjusted to serum cholesterol. Plant stanols reduced LDL-C by 10% from controls (P<0.05), but PCSK9 levels were unchanged and did not differ between the groups.
A double-blind cross-over design. (De Smet et al., 2015)	14 subjects (eight female and six male; age 21–55 years), with a BMI ranging from 21 to 29 kg/m2	Consumed in random order a shake with or without plant stanol esters (4 g).	No adverse effects reported.	At 5 h after consumption of the shake, biopsies were taken from the duodenum (around the papilla of Vater) and from the jejunum (20 cm distal from the papilla of Vater)	Microarray analysis showed that the expression profiles of genes involved in sterol metabolism were not altered. Surprisingly, the pathways involved in T-cell functions were down-regulated in the jejunum. Immunohistochemical analysis showed that the number of CD3 (cluster of differentiation number 3), CD4 (cluster of differentiation number 4) and Foxp3þ (forkhead box P3-positive) cells was reduced in the plant stanol ester condition compared with the control condition, which is in line with the microarray data.
Multi-centered, randomized, controlled, double-blind, parallel trial. (Sola et al., 2012)	113 subjects age range 43-65 years pre-hypertensive, stage-1 hypertensive and hypercholesterolemic	One of 4 cocoa cream products (13 g/unit; 1 g cocoa/unit, 6 units/d; 465 Kcal/d) added to a low saturated fat diet for 4 weeks. The groups were: A) cocoa cream considered as control; B) cocoa+hazelnut	No adverse effects reported.	Primary outcome measures were BP, LDL-c, apolipoprotein B-100 (Apo B), ApoB/ApoA ratio, oxidized LDL (oxLDL) and high-sensitive C-reactive protein (hsCRP) determined at baseline and post-cocoa cream product intake.	After 4 weeks, compared to product A, product C reduced LDL-c by 11.2%, Apo B by 8.1% and ApoB/ApoA ratio by 7.8% (P = 0.01). LMN decreased LDL-c by 9.2%, Apo B-100 by 8.5%, ApoB/ApoA ratio by 10.5%, hsCRP by 33.4% and oxLDL by 5.9% (P = 0.01). Surprisingly, even ‘‘control’’ product A reduced systolic BP (27.89 mmHg; 95%CI:

Type of study (reference)	Subject details	Treatment details (dose, duration, route)	Adverse reactions and safety indicators	Endpoints	Key outcomes
		cream (30 g/d hazelnuts); C) cocoa+hazelnuts+ phytosterols (2 g/d); and D) cocoa+hazelnuts+ phytosterols+solu ble fiber (20 g/d) the patented ‘‘LMN product’’.			211.45 to 24.3) and diastolic BP (25.54 mmHg; 95%CI: 27.79 to 23.29). The BP reductions were similar with the other 3 products.
Randomized double-blind crossover, placebo-controlled study. (Vasquez-Trespalacios & Romero-Palacio, 2014)	40 hypercholestero lemic subjects aged between 20 and 50 years old.	Subjects consumed Benecol® yogurt drink (4g of plant stanols as esters,) and the other control consumed placebo yogurt during four weeks	No adverse effects reported.	Blood Lipids	Yogurt drink with added plant stanols (4 g) as esters (Benecol®, Colanta) consumption compared to regular yogurt drink caused a statistically significant decrease in total cholesterol and low density lipoprotein cholesterol by 7.2% and 10.3%. During the two periods and compared to controls, high-density lipoprotein cholesterol and triglycerides were not significantly different.

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