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Review

Phytosterols and cardiovascular health

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ABSTRACT

Phytosterols are typical constituents of plants' cell walls. When ingested with plant foods, they reduce cholesterol absorption from the gut, due to their structural similarity with cholesterol. In the last decades, purified plant sterols or stanols have been added to various foods items to obtain functional foods with remarkable hypocholesterolemic activity. A daily intake of plant sterols or stanols of 1.6–2 g/day, incorporated in these foods, is able to reduce cholesterol absorption from the gut by about 30%, and plasma LDL cholesterol levels by 8–10%. Since the action of plant sterols or stanols on plasma LDL cholesterol is additive to that of statins, the former can be used to increase the latter's hypocholesterolemic action in patients needing a marked reduction in plasma LDL cholesterol levels. Phytosterols, up to 3 g/day, are safe and effective cholesterol-lowering agents.

Contents

1. Introduction

Non-pharmacological control of plasma lipid profile is being actively explored with the use of a variety of agents/nutrients/nutraceuticals/functional foods [1–3]. Among such agents, phytosterols are being widely employed and are part of several food items and supplements.

The hypocholesterolemic effects of phytosterols (plant sterols and stanols, PS) have been known since about 1950, when a fall of about 27% was observed in the plasma cholesterol levels of 26 healthy subjects supplemented with 5–10 g/day of PS, for 2 weeks. Subsequent studies demonstrated that high doses of PS (over 10 g/day), taken for 3–5 weeks, were able to decrease blood cholesterol levels, on average, up to 20% [4].

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The doses of PS recommended to reduce blood cholesterol, consequently, ranged between 9 and 30 g/day up to the late '70s. The first PS preparations were quite heterogeneous in terms of both composition and source, but they all appeared to be effective and safe. Their pharmacological application was limited, at those times, to severe hypercholesterolemias, mainly due to the elevated cost of high-purity compounds.

Calculations of the large amounts of PS in the ancestral diet stimulated research on their role in human health, notably with the aim to correct the low intake of these compounds in modern diets. Hence, PS shifted from being natural food components to being formulated into medications and supplements or incorporated in conventional foods. Firstly, they were incorporated into lipid-based products, mostly margarines. Subsequently, the progress of food technologies has allowed to improve their solubility and incorporation in different food products such as fruit juice, ice cream, oven baked products, etc. [5].

2. Biochemistry

Like cholesterol, to which they are related both structurally and biosynthetically, PS belong to the family of triterpenes, with a tetracyclic ring and a side chain linked to carbon 17. They can be classified into sterols and stanols, according to the presence or absence of a double bond at the Δ5 position. PS exist in free or esterified forms: free sterols form part of the cellular wall, where they play important structural functions, whereas sterol esters represent storage products within the cell [6] (Fig. 1).

More than 250 different PS molecules have been identified to date; β-sitosterol is the most abundant among them. The only structural difference between sitosterol and cholesterol consists of an additional ethyl group present at position C-24 in sitosterol, which is probably responsible for its poor absorption. Other plant sterols such as campesterol, stigmasterol, and dihydrobrassicasterol are present in vegetal foods at much lower concentrations; the saturated derivatives campestanol and sitostanol are found in almost negligible amounts in plants [7]. In turn, the most common dietary PS are sitosterol, campesterol, and stigmasterol, that contribute to about 98% of the total dietary intake.

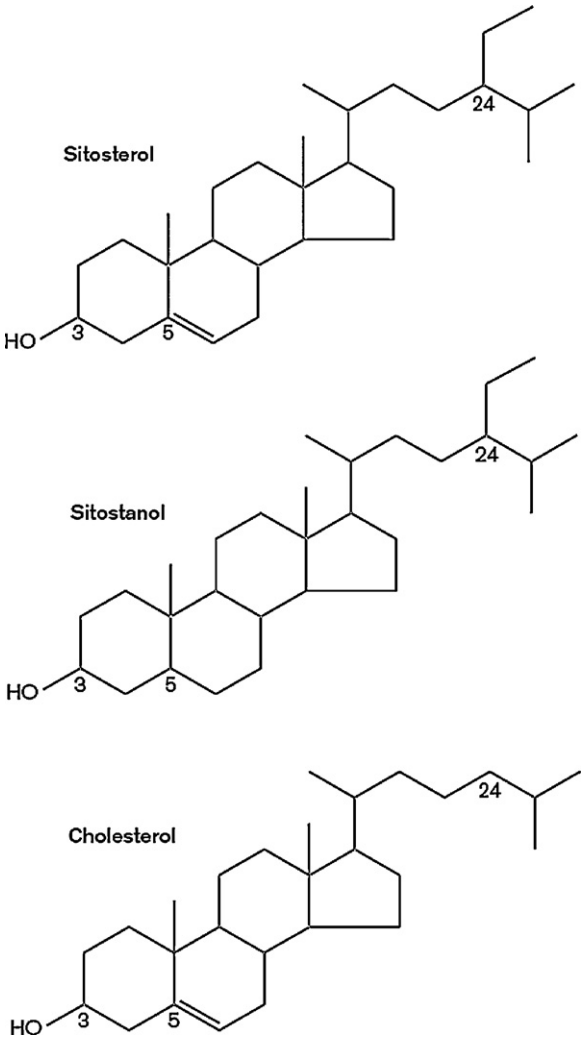

Fig. 1. Structures of sitosterol and sitostanol.

3. Dietary sources and intake

The main PS sources are vegetable oils, nuts, grains, and grain-derived products; also sprouts, cabbages, cauliflowers, green and black olives contain plant sterols and stanols (Table 1). Among non-vegetable foods, egg yolks, mammalian liver and crustaceans represent important sources of PS in Western diets. In walnuts, PS represent 0.1–0.2% of the total lipid fraction; about 87% of the total PS is represented by sitosterol. Macadamia nuts contain about 1.3 mg of PS per gram of lipids [8].

The major sources of plant sterols used for incorporation into commercial products are tall oil – which contains up to 80% β-sitosterol – and the by-products of soybean oil production. Both sterols and stanols are frequently used in esterified forms, as fatty acid esters: this increases their solubility and allows their incorporation into lipid-based foods [7].

Due to large differences in the consumption of plant foods throughout the world, the dietary intake of PS ranges from 167 mg/day in Britain (mainly from vegetable oils) to 375 mg/day in Japan [9]. However, it varies greatly also within Western population groups, being markedly higher (+50%) in vegetarians. In the large sample of the EPIC study (European Prospective Investigation into Cancer), performed on 22,256 subjects, PS intake ranged from 463 mg/day (highest quintile) to 178 mg/day (lowest quintile) [10,11]. The dietary intake of plant stanols is much lower, about 50 mg/day [10].

As PS cannot be endogenously synthesized by humans, their circulating levels are only dependent upon diet and absorption efficiency. Miettinen and coworkers [12] found a positive correlation between the circulating concentration of campesterol and sitosterol and the amount of dietary PS ingested, as well as the polyunsaturated/saturated fatty acid ratio of dietary fat and the linoleic acid contents of plasma and dietary lipids. Depending on the type and amount of plant foods consumed, PS consumption, and therefore PS blood levels, may vary greatly within and between populations.

Results from intervention studies suggest that higher PS intake in the form of supplements increases circulating levels of PS, while plant stanol supplementation decreases them [9].

Inter-individual variability affects phytosterols' absorption: it is known that the absorption route of PS is similar to that of cholesterol, whose efficiency is affected by ApoE polymorphisms. Therefore different ApoE phenotypes may modify plasma concentrations of PS, even if data from studies in different populations are inconsistent and not as yet conclusive. However, it is likely that the ApoE phenotype plays a role in explaining why variations in PS concentrations exist within and across different population groups [13].

Table 1
Mean content of sterols and stanols in some vegetable foods (mg/100 g).

Food	Total phytosterols (mg/100 g)[a]
Oils and fats	
Wheat germ oil	919
Corn oil	909
Rapeseed oil	668
Sunflower oil	411
Soybean oil	320
Peanut oil	258
Grape seed oil	215
Margarine	217 (92–721)
Olive oil	154
Palm oil	39
Nuts and seeds	
Sesame seeds	360
Sunflower seeds	300
Pistachio nuts	276
Almonds	183
Hazelnuts	138
Walnuts	127
Peanuts	104
Cereals	
Wheat germ	344
Wheat bran	200
Buckwheat flour	99
Whole wheat bread	86
Rye flour	86
Whole wheat flour	70
Wheat	69
Rye	69
Crackers	67
Muesli	63
Orn flour	52
Bread	44
Rice	30
Wheat flour	28
Rice flour	23
Corn flakes	22
Puffed rice	20
Fruits	
Passion fruits	44
Oranges	24
Figs	22
Lemmons	18
Grapefruits	18
Pineapples	17
Clementines	16
Peaches	15
Apples	13
Pears	12
Kiwi	9
Melons	2
Watermelons	1
Vegetables	
Black olives	50
Bruxelles sprouts	43
Cauliflowers	40
Broccoli	39
Green olives	35
Mushrooms	18
Celeries	17
Carrots	16
Fennels	10
Onions	8
Leeks	8
Peppers, green	7
Tomatoes	5
Boiled potatoes	4

[a] Sum of sitosterol, campesterol, stigmasterol, sitostanol and campestanol.

4. Metabolism

4.1. Absorption

The first studies, carried out at the beginning of the last century, indicated that PS were not significantly absorbed by humans. More recently, the administration of deuterium-labelled PS to human subjects has allowed assessing the quite low, but different, absorption rates of the various components. These rates range from about 0.5% to 1.9% for sitosterol and campesterol, respectively; the figures for the corresponding saturated PS are reduced by approximately an order of magnitude (0.044% for sitostanol and 0.155% for campestanol) [7].

Heinemann et al. [14] demonstrated that the rate of intestinal absorption of PS is inversely associated with the side chain length: under normal conditions, PS with a long side chain are minimally absorbed as compared with cholesterol.

The absorption sequence is similar for both cholesterol and PS. Both these sterols are solubilized in mixed micelles, after the hydrolyzation of esters by a pancreatic ester hydroxylase. The enterocyte is penetrated by either passive diffusion or by a receptor-mediated process. The putative specific carrier of cholesterol and PS is NPC1L1, a trans-membrane transport protein that was recently described [15]. Indeed, selective NPC1L1 blockade by ezetimibe halves both cholesterol and PS absorption [16].

The PS side chain is responsible for the selective secretion of sitosterol and other PS from the enterocyte into the intestinal lumen, mediated by the adenosine triphosphate (ATP) binding cassette (ABC) transporters ABCG5 and ABCG8 [7]. Recent findings suggest that ABCG5 and ABCG8 play a role also in the biliary secretion of sterols.

Within the mucosa, a fraction of PS is re-esterified by the ACAT. The intestinal esterification of sterols by ACAT was reported to be significantly less efficient for PS than for cholesterol [17].

As a consequence, plasma levels of PS in humans are normally about 0.5% of those of cholesterol, reflecting both the high endogenous cholesterol synthesis in the liver and the less efficient absorption of PS by the small intestine. Plant stanols concentrations in plasma are only 0.05% that of cholesterol [18].

4.2. Distribution and excretion

Absorbed PS are transported to the liver via chylomicrons, as is cholesterol. In experimental models, however, only 12% of PS (as compared to 70–80% of the absorbed cholesterol) is transported in the esterified form in the chylomicrons. Free PS are carried as surface lipids in these particles.

Once taken up by the liver from the chylomicrons remnants, PS are secreted into blood as constituents of VLDL particles. The percentage of esterified PS and esterified cholesterol in VLDL and LDL is essentially identical. HDL, on the opposite, have a higher PS/cholesterol ratio in comparison with LDL and VLDL, suggesting that PS are preferentially carried by these particles. Together with the observations that the HDL-associated PS seem to be selectively secreted into bile and that the PS/cholesterol ratio is usually higher in bile than in plasma, these data indicate that HDL lipoproteins play an important role in the removal of PS from the body [19].

At the cellular level, PS are stored in the cytoplasm or incorporated into the cell membrane. They play no known biological or functional role [17].

Excretion of absorbed PS takes place primarily via the biliary route, while a minor fraction is excreted through the skin. Together with lower absorption, PS's excretion is rapid and responsible for the fact that endogenous pool size of PS are smaller than those of cholesterol.

Data on bile acids biosynthesis from PS are conflicting. Recent evidence indicates that, after losing their side chain, they are catabolised – like cholesterol – in the different organs [17].

5. Mechanisms of hypocholesterolemic activity

PS intake with food decreases intestinal cholesterol absorption, eventually inducing a reduction in plasma total and LDL cholesterol concentrations [19]. Early studies showed that plant stanols were more effective in decreasing cholesterol absorption than sterols, suggesting a greater cholesterol-lowering effect [10]. More recently, however, the effect of plant sterol and stanol esters – incorporated in butter or margarine – on cholesterol absorption and, consequently, on plasma cholesterol levels, has been shown to be comparable. Interestingly, PS have a reduced capacity to suppress HMG-CoA reductase activity as compared to cholesterol. This is in accordance to the finding that the cholesterol-lowering effect of PS does not involve suppression of the endogenous cholesterol synthesis.

The principal mechanisms of PS-induced reduction in cholesterol absorption have been elucidated. In brief, PS compete with cholesterol molecules for incorporation into mixed micelles in the intestinal tract. A co-crystallization with cholesterol, yielding an increased fecal excretion of cholesterol, takes also place.

A few studies suggest that similar effects can be obtained by administering PS in a single dose or divided into the 3 meals; this suggests that the daily intake pattern does not affect PS efficacy on plasma cholesterol levels, and that the reduced incorporation of cholesterol into mixed micelles may only partially be responsible for the cholesterol-lowering effect of PS assumed with meals. Plat and Mensink have proposed that PS enter the enterocytes, thereby affecting intestinal lipoprotein metabolism [19]. In contrast to cholesterol, PS are only minimally esterified, incorporated, and secreted into the circulation via the chylomicrons.

As compared with cholesterol, PS are more readily hydrolyzed. This process leads to a lower solubilization of cholesterol into micelles, decreasing its absorption and, in turn, increasing fecal excretion of cholesterol and its metabolites.

PS may affect cholesterol levels also through the upregulation of the ATP-binding cassette transporters ABCG-5 and ABCG-8, located at the apical surface of the enterocyte.

6. Association between PS intake and plasma cholesterol levels: epidemiological evidence and clinical trials

The effect of PS on blood cholesterol has been extensively studied in humans. In observational studies, performed in Northern Sweden and in Great Britain, free living subjects in the top quintiles of PS intake with food have a significantly lower plasma total and LDL cholesterol as compared to subjects in the lowest intake quintile [11,20].

Significant reductions of LDL cholesterol levels have also been obtained in most of randomized clinical trials performed using PS in humans. The dose–effect relationship starts to exhibit significant hypocholesterolemic effects at intakes of about 500 mg/day (in good accordance with the epidemiological evidence previously described). This effect is increased for daily intakes in the range 500–2500 mg/day, while for greater intakes the effect on LDL cholesterol levels seems to level off [21].

A recent meta-analysis has considered 59 selected randomized placebo-controlled studies, conducted to test the efficacy of interventions lasting 2 or more weeks (with PS incorporated into food matrices), on circulating cholesterol levels in adults [22]. In the overall pooled estimate on about 4500 subjects, LDL levels significantly decreased by 0.31 mmol/L on the average, compared with placebo, despite the great clinical and methodological heterogeneity observed between the trials. The splitting of subjects into two groups according to the baseline LDL cholesterol concentrations, defined low and high according to ATP III, has allowed noting that the greater LDL reduction occurred in individuals with optimal initial levels. These results were recently discussed by Demonty et al., who analyzed 84 trials and concluded that "Higher baseline LDL-C concentrations resulted in greater absolute LDL-C reductions" [23]. A less recent study from Katan et al. [21] has concluded that the placebo-adjusted reduction in LDL cholesterol associated with PS rises with age, probably due to the progressive increase of the baseline levels, even though the percentage reduction was not significantly different in younger vs. older people.

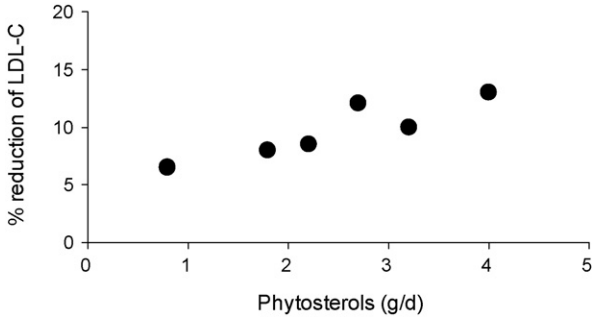

Fig. 2. Estimates of low-density lipoprotein cholesterol (LDL-C) percentage reductions as recorded in randomized placebo-controlled trials. The ranges of daily doses shown (number of trial arms in parentheses) are 0.7–1.1 g (8), 1.5–1.9 g (13), 2.0–2.4 g (14), 2.5–2.9 g (5), 3.0–3.4 g (13), and 4.0–4.2 g (2). Adapted from Katan et al. [21].

The results of a metanalysis published by Abumweis [22] confirm the dose–response effect of PS, at doses ranging from 1.5 g to 2.5 g/day, as already shown by Katan (Fig. 2). Little additional effects were recorded at doses higher than 2.5 g/d. However, the 5–10% effect estimated while testing doses of 0.7–1.1 g/d suggests that about half the effect observed with higher amounts may be attained at this dose.

Data from short- and long-term trials indicate that the cholesterol-lowering effect of PS is noticeable within few weeks and that it remains stable for up to 1 year of supplementation. In particular, the administration of plant sterols with margarines at doses of 1.5 and 3 g/day for 6 months induced the same reduction in both total (−8.9% vs. −8.3%) and LDL cholesterol (−11.3% vs. 10.6%) [19]. However, interruption of regular intakes may halt the effects of PS, bringing cholesterol concentrations back to basal conditions.

As already mentioned, the hypocholesterolemic effect of PS may also be affected by the frequency and the time of their intake. Concerning frequency, the same intake of PS esterified in margarines, consumed once per day at lunch or divided over three portions resulted in similar LDL lowering effects [24].

In a recent study, the intake of PS with or without food was compared. The results suggested that their consumption with food may increase their metabolic effects (see below) [25].

The use of PS in diabetic patients has also been the subject of a systematic review of the literature [26]. From the 18 studies considered, 5 clinical trials with sterol-fortified margarines ($n = 4$) and granola bars ($n = 1$), involving 148 subjects treated for 3–12 weeks, were included in the meta-analysis. According to the results, the supplementation of diabetic patients with 1.6–3 g/day of plant sterols/stanols significantly reduced total and LDL cholesterol (−10.3 mg/dL and −12.2 mg/dL on average, respectively), without affecting triglyceride levels. HDL-cholesterol levels tended to increase, but the effect was not statistically significant. Although

these observations need further confirmations by longer term clinical trials on larger groups of patients, they are of clinical relevance, especially according to the indication that each 1% reduction in LDL cholesterol corresponds to a 1% reduction in CHD relative risk, especially for subjects at high cardiovascular risk, like those affected by type 2 diabetes.

7. Phytosterols and foods

The efficacy of PS in cholesterol lowering have been tested predominantly by incorporating them into either regular or low fat spreads [27]. Both plant sterols and stanols have been integrated into low fat milk and yoghurt, bakery products, orange juice, cereal bars, low and non-fat beverages, chocolate. The impact of different food compositions on the hypocholesterolemic effect of PS has not yet been completely clarified, due to the great variability of data from clinical trials carried on with the same food carrier. Abumweis and coworkers [22] have classified all the 59 considered studies according to the fat content and the physical form of the different food carrier used for the administration of PS into four groups: fat spreads, mayonnaise and salad dressing, milk and yoghurt and others (including chocolate, cereal bars, beverages, juices, meat and oven baked products). The incorporation into spreads, mayonnaise/salad dressing, milk/yoghurt, was associated with a greater efficacy in LDL cholesterol reduction than incorporation into other foods, suggesting the important role of the food matrix in affecting the cholesterol-lowering effect. In particular, it has been demonstrated that plant stanol esters with low fat milk are almost three times more effective than with bread and breakfast cereals [28].

8. Safety

The US Food and Drug Administration and the European Union Scientific Committee have thoroughly reviewed the safety of phytosterols, phytostanols, before and after approving their use in functional foods.

8.1. Toxicity

The first toxicity study was performed with PS preparations to be marketed in the 1950s for cholesterol lowering, containing from 65 to 90% of sitosterol. No detectable effects were observed in rats, rabbits, and dogs fed large amounts of PS over a 2-year period with regard to growth, serum proteins, blood urea nitrogen, gross and microscopic appearance. Afterwards, the lack of toxicity and genotoxicity has been assessed for PS in rats fed mixed PS at levels of 0.1–5.0% (wt/wt) for 90 days [29].

No effect has been observed for PS (sterols and stanols) esters on levels of reproductive hormones in women and on fecal bacterial enzymes or short-chain fatty acids in healthy volunteers [29].

8.2. Effects on plasma carotenoids

The consumption of PS (stanols and sterols) has been associated with a reduction in plasma levels of fat-soluble vitamins, probably the result of a reduction in the lipoproteins which are the vitamin carriers in plasma [21]. A meta-analysis has shown that circulating concentrations of vitamins A, D and E, alpha carotene and lycopene are not affected by PS after adjustment for LDL plasma levels [21]. An increase in consumption of carotenoids sources (carrots, pumpkins, apricots, spinach, broccoli), moreover, seems to be able to balance the plasma carotenoid reduction following PS supplementation [30].

Beta carotene plasma levels, after PS consumption, are on the other hand significantly reduced also after adjusting for the lipoprotein effect. However, the addition of carotenoids to the diet in the form of the recommended 5 servings of fruit and vegetables per day effectively maintains carotenoid levels in the normal range in subjects supplemented with PS [31]. Studies on subjects supplemented with PS incorporated in spreads or bread and cereals have demonstrated that increasing the consumption of fruits and vegetables is enough to correct and to maintain circulating carotenoid levels [31]. The issue of carotenoid lowering by PS has also been addressed in lactating women, but its consequences on infant development are still to be elucidated [32].

In 2002, a document of the Scientific Committee on Food of the European Commission "recommends the use of natural sources of β-carotene, i.e. carotenoid-rich vegetables and fruits, to counterbalance the expected reduction of blood β-carotene and other fat-soluble nutrients levels caused by long-term consumption of foods enriched in phytosterols" [33].

In 2004, the European Commission adopted specific rules for labeling "foods and food ingredients with added phytosterols, phytosterol esters, phytostanols and/or phytostanol esters" in Commission Regulation (EC) No. 608/2004 and stated that "this food should be part of a balanced diet, including regular consumption of fruits and vegetables to help maintain plasma carotenoids levels" [34].

8.3. Sitosterolemia (phytosterolemia)

Sitosterolemia is a rare inheritable autosomal recessive disease, associated with mutations in only one of ABCG5 and ABCG8, the half-transporters which play an important role in regulating intestinal plant sterol absorption by excreting plant sterols that have already been taken up from the enterocyte back into the intestinal lumen [9,35]. Some of the mutations in ABCG5 and ABCG8, identified in families with sitosterolemia, result in truncated proteins that lack normal functionality.

Studies on ABCG5/ABCG8-deficient mice have demonstrated that knockout animals have higher concentrations of non-cholesterol sterols, suggesting that ABCG5 and ABCG8 are necessary to maintain cholesterol in cell membranes [36]. The lower concentrations of sterols in the bile, despite the higher hepatic cholesterol concentrations, indicate that the lack of ABCG5 and ABCG8 is associated with the loss of preferential sterol secretion in the bile.

Sitosterolemia is, in fact, characterized by non-selective sterol hyperabsorption, including plant and shellfish sterols, leading to the development of xanthomas and premature CHD [37]. Patients with sitosterolemia absorb between 15 and 60% of the ingested sitosterol, compared to less than 5% absorbed in normal subjects. In these subjects, the intestinal absorption of dietary cholesterol is enhanced too, as the secretion of cholesterol into the bile.

As a result of the increased intestinal uptake and the decreased hepatic secretion, plasma concentrations of PS and other neutral sterols are approximately 50–100 times higher than that in healthy subjects.

For this reason, dietary PS are contraindicated in homozygous sitosterolemic patients, whose circulating levels could be further elevated. In general, it has been demonstrated that the intake of 2–3 g/d of plant sterols elevates serum sitosterol and campesterol concentrations by 30% and 70%, respectively, in healthy subjects, and by 50% and 125%, respectively, in heterozygous sitosterolemic patients, suggesting that only one functional ABCG5 or ABCG8 allele is sufficient for nearly normal function.

Sitosterolemia is also associated with lower activity of HMG-CoA reductase and other enzymes involved in the cholesterol biosynthesis pathway and with the increased expression of the LDL receptor, resulting in suppressed cholesterol levels [38].

Aside from sitosterolemia, several common sequence variations have been described, determining the plasma campes-

terol/cholesterol and sitosterol/cholesterol ratios, as well as PS plasma concentrations. In brief, clarification of the gene-regulated interaction between cholesterol (and PS) metabolism and vascular function and structure will help tailoring the appropriate supplementation [39].

8.4. Phytosterol plasma levels and atherosclerosis

The development of premature CHD in several individuals with sitosterolemia suggests that the presence of high serum PS levels may be particularly atherogenic. However, the association between elevated serum plant sterol levels and the incidence of CHD registered in a large population study [40] has not been confirmed in two other case-control studies of similar characteristics [41,42]. Electron beam computer tomography in 2542 subjects aged 30–67 has revealed that plasma levels of cholesterol, but not sitosterol or campesterol, were significantly higher in the presence of coronary calcium, not supporting the relationship between elevated plasma PS levels and atherosclerosis. Furthermore the degree of risk associated with serum PS levels in otherwise normal individuals is much below the levels observed in patients with sitosterolemia [43].

It has been proposed that increased absorption of plant sterols, resulting from higher intakes, may increase the risk of atherosclerosis; however, the intake of PS in gram quantities, as a dietary therapeutic approach to hypercholesterolemia, increases PS plasma levels to values 20–100 times lower than those observed in patients with sitosterolemia, still within the normal physiologic range [44].

The evidence on the relationship between PS intake and the risk of developing atherosclerosis has been summarized in recent reviews [9,44], in which the available data in favor and against PS as an atherosclerotic risk factor have been analyzed. In brief, an association between the increase in circulating PS and CHD risk has been hypothesized by observational studies (prospective cohort studies, case-control studies) [21]. As of today, there are no controlled intervention studies that have addressed this issue. We propose that the potential risk of PS enriched foods may be counterbalanced by their efficacy in reducing LDL cholesterol, a more relevant cardiovascular risk factor, whose reduction is associated with a decrease in CHD risk. In any case, only prospective intervention trials would eventually fully resolve this issue.

It should be noted that a recent paper by Weingartner et al. [45] reported increased plasma sterols concentrations correlating with increased atherosclerosis in apoE$^{-/-}$ mice fed a Western diet supplemented with PS. The same authors noted increased plasma concentrations and 5-fold higher sterol concentrations in aortic valve tissue of patients consuming PS. In turn, studies with clinical endpoints are lacking and, at present, we have to rely on surrogate markers such as cholesterolemia.

9. Combination with drugs

The additive hypocholesterolemic effect of phytosterol to statins has been firstly demonstrated with high doses: 5.1 g/day of plant stanols/sterols produce an additional 15% reduction in LDL concentrations [46].

The effects of phytosterols for patients receiving statins have been confirmed by double-blind, randomized, placebo-controlled trials using both stanols and sterols in doses of 2–3 g/day for 4–8 weeks and resulting in LDL cholesterol reduction of 7–11% [47]. The magnitude of the additional decrease in LDL cholesterol was slightly lower than that which would be expected from quadrupling the statin dosage.

Other lipid-lowering agents, notably ezetimibe, have also been investigated in combination with PS. Assman et al., showed decreased PS absorption during ezetimibe treatment [48]. Indeed, the two agents share similar mechanisms of action and might compete with each other for cholesterol and PS absorption: Jakulj et al. showed no additional benefit of PS addition to ezetimibe treatment [49]. Studies in mice [50] did not prove synergistic effects of a combination fibrates-PS, which remains to be fully explored, even though Nigon et al. reported a mild additive effect of PS supplementation [51].

10. Conclusions

In conclusion, plant sterols and stanols consumed with habitual foodstuffs are generally recognized as safe and adverse effects of their use seem to be very unlikely in adults [29]. The available evidence demonstrates that the consumption of about 1.6–2 g/d of sterols and stanols, preferably dissolved in a fat rich food matrix, and consumed at the end of a meal, is effective in lowering LDL cholesterol levels by 10%. This reduction may correspond to a fall of CHD risk by 12–20% in the following 5 years, though this hypothesis needs confirmation and trials with clinical endpoints are lacking.

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