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Review article

The position of functional foods and supplements with a serum LDL-C lowering effect in the spectrum ranging from universal to care-related CVD risk management

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HIGHLIGHTS

- Prevention of CVD can be achieved through healthy lifestyle and optimal improvements in LDL-C levels.
- Functional foods and food supplements with proven efficacy on plasma LDL-C levels can help achieve better lipid control.
- Functional foods can be used for prevention in the general population and prevention in patient populations.
- There is a discussion whether LDL-C lowering is sufficient to state that a particular (functional) food lowers CVD risk.
- Decision-sharing with patients is important for empowerment of preventive actions and adherence to diet and lifestyle.

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ABSTRACT

A wealth of data demonstrates a causal link between serum low-density lipoprotein cholesterol (LDL-C) concentrations and cardiovascular disease (CVD). Any decrease in serum LDL-C concentrations is associated with a decreased CVD risk, and this benefit is similar to a comparable LDL-C reduction after drug treatment and dietary intervention. Moreover, life-long reductions in serum LDL-C levels have a large impact on CVD risk and a long-term dietary enrichment with functional foods or supplements with a proven LDL lowering efficacy is therefore a feasible and efficient approach to decrease future CVD risk.

Functional foods with an LDL-C lowering effect can improve health and/or a reduce the risk of disease. However, it has not been mentioned specifically whether this concerns mainly universal prevention or whether this can also be applied to the hierarchy towards care related prevention. Therefore, we here describe the effects of a list of interesting functional food ingredients with proven benefit in LDL-C lowering. In addition, we pay particular attention to the emerging evidence that the addition of these functional ingredients and supplements is advisable as universal and selective prevention in the general population. Moreover, functional ingredients and supplements are also helpful in care related prevention, i.e. in patients with elevated LDL-C concentrations who are statin-intolerant or are not able to achieve their LDL-C target levels. Furthermore, we will highlight practical aspects regarding the use of functional foods with an LDL-C lowering effect, such as the increasing importance of shared decision making of medical doctors and dieticians with patients to ensure proper empowerment and better adherence to dietary approaches. In addition, we will address costs issues related to the use of these functional foods, which might be a barrier in some populations.

1. Introduction

Atherosclerotic cardiovascular disease (ASCVD) remains one of the leading causes of death and disability-adjusted life-years [1–3]. The decline in cardiovascular death observed during the past four decades in Western Europe is less impressive in middle-income countries where cardiovascular disease (CVD) remains the leading cause of death. Furthermore, such decline might be offset in the next decade by an increase of prevalence in obesity and subsequent dyslipidemia and diabetes.

High serum levels of low-density lipoprotein cholesterol (LDL-C) are

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clearly linked to the risk of ASCVD and several comprehensive reviews demonstrated the causal link between LDL-C and ASCVD [4,5]. Despite the rather short period of intervention trials notably with statins (usually < 5 years), a 1.0 mmol/L reduction in LDL cholesterol was associated with a reduction of major vascular events in both women (rate ratio [RR] 0.84, 99% CI 0.78–0.91) and men (RR 0.78, 99% CI 0.75–0.81) [6,7]. A meta-analysis of all drug and dietary trials demonstrated that the benefit for a similar reduction in LDL-C is similar with both strategies [8]. Life-time reductions in serum LDL-C levels have a huge impact on CVD at a populational level. Indeed, LDL-C reductions are associated with a dramatic decrease in CVD risk in subjects with a loss-of-function *PCSK9* gene mutation [9]. Of the 3363 black subjects examined in the study, 2.6% had nonsense mutations in *PCSK9*, with a 28% reduction in LDL-C and an 88% reduction in the risk of coronary heart disease (CHD), while of the 9524 white subjects, 3.2% had a sequence variation in *PCSK9* that was associated with a 15% reduction in LDL-C and a 47% reduction in the risk. Similarly, small changes in LDL-C have a strong impact on calculated life-time risk [10]. Furthermore, a large study conducted in the US population demonstrated that a major decline (44%) of deaths from CHD could be attributed to changes in risk factors [11]. Interestingly, 24% decrease of the coronary deaths was due to a 6% reduction in total cholesterol (TC).

Finally, the most recent data show that prevalence of hypercholesterolemia is high in Europe [2]. The mean age-standardized prevalence of hypercholesterolemia (above 6.2 mmol/L or 242 mg/dl) averaged across member countries was 16.4% and 15.8% in women and men. Data for 2009 showed that the mean blood cholesterol concentration across European countries was 5.1 mmol/L (200 mg/dl) in both women and men. The difference of cholesterol levels between countries with lowest and highest values is approximatively 1 mmol/l (39 mg/dl). As a consequence, a long-term dietary approach and LDL-C decrease with functional foods would be a unique opportunity to significantly decrease CHD risk throughout a lifetime.

In the recent European recommendations, patients are classified according to the 10-year risk of cardiovascular death [12]. The Systematic Coronary Risk Evaluation (SCORE) is derived from a large dataset of prospective European studies and is based on gender, age, total cholesterol, systolic blood pressure and smoking status. In subjects at low cardiovascular risk with LDL-C below 190 mg/dl and above 116 mg/dl, treatment with statins is not immediately recommended. Patients below 40 years are out the range of the SCORE equation and except those with familial hypercholesterolemia or severe risk factors, have a low risk. All these patients might benefit from functional foods on top of usual dietary advice when they do not meet LDL-C target levels. This indicates that functional ingredients and supplements could have a major impact on LDL-C levels in both universal prevention and care-related settings. On top of risk evaluation, the choice of each patient has a major impact. Patients reluctant to start statin may be less adherent and may also have more nocebo effect. For these patients, a combination of classical dietary advice and LDL lowering functional foods or supplements is an attractive approach. Similarly, patients upon treatment not achieving their LDL-C target might also benefit from further reduction of LDL-C through functional foods or supplements. Since CVD risk is determined by other factors besides LDL-C concentrations, a prerequisite for the use of functional foods and supplements is that they do not negatively impact other CVD risk markers, such as weight gain or blood pressure. In the last decades, consumer demand for health-enhancing food products, such as functional foods, has grown rapidly. In this review, we will present evidence showing the impact of different functional food ingredients on LDL-C, advantages and limitations in the use of these ingredients and suitable candidates who might benefit from functional ingredients and supplements. Moreover, we will especially focus on their position, i.e. is this only universal prevention or can this also be applied to the hierarchy towards care related prevention? Finally, we will highlight some practical aspects of the use of functional foods with an LDL-C lowering effect, such as the increasing importance of shared decision making of medical doctors and dieticians with patients to ensure proper empowerment and better adherence to dietary approaches, and we will address costs issues related to the use of these functional foods, which might be barriers in some populations.

2. Functional ingredients and supplements that can lower LDL-C

Functional foods have specific physiological advantages that distinct them from regular foods. Although different definitions exist, one of the most common used definitions arises from the EU-project Functional Food Science in Europe (FUFOSE), which regards a food as functional when 'it has satisfactorily demonstrated to affect beneficially one or more target functions in the body, beyond adequate nutritional effects, in a way that is relevant to either an improved state of health and well-being and/or a reduction of risk of disease' [13]. Dietary supplements or nutraceuticals (classification in America) are made from food, isolated nutrients or food-like substances, and appear as pills, powders, potions and other medicinal forms that are generally not associated with food [14]. In this review, we discuss several functional foods and dietary supplements with LDL-C lowering abilities and an overview of these functional foods with their average LDL-C reduction and level of evidence is provided in Table 1.

Foods enriched with plant sterol or plant stanol esters are one of the first examples of functional foods that demonstrated a clear reduction in TC and LDL-C concentrations. Plant sterols and plant stanols are naturally occurring constituents of plants and are found in vegetable oils, such as corn oil, soybean oil, and rapeseed oil and they are also present in cereals, nuts, fruit and vegetables. The average intake of plant sterols and plant stanols in Western countries is approximately 300 mg/day, but can be as high as 600 mg/day in vegetarians [15]. Serum plant sterol and plant stanol concentrations are the result of intestinal absorption and biliary secretion, which leads to serum concentrations of plant sterols and plant stanols that are less than 1% of that of serum cholesterol [17]. The LDL-C lowering effect of plant sterols and plants stanols is demonstrated in numerous studies resulted in the recommendations to consume plant sterol and plant stanol enriched products in current dietary guidelines [12,18]. Plant sterols or plant stanols reduce serum LDL-C concentrations by competing with cholesterol for incorporation into micelles in the gastrointestinal tract, resulting in an increased endogenous cholesterol synthesis rate and an up-regulation of LDL-receptor expression. Large meta-analyses showed that consuming approximately 2.5 g/day of plant sterols or plant stanols lowers serum LDL-C concentrations up to 10%. At doses up to 3.0 g/day, plant sterols and plant stanols have a comparable LDL-C lowering efficacy, while there are discrepancies between the efficacy of

Table 1
Functional ingredients and supplements with proven or claimed efficacy on LDL-C levels: average LDL-C reduction and level of evidence.

Functional ingredient/supplement	Magnitude of effect[a]	Levels of evidence[a]
Plant sterols and plant stanols	+ +	A
Red yeast rice	+ +	A
Soluble fiber	+	A
Soy protein	+	B
Probiotics	+	C
Berberine	+	C
Bergamot	+	C
Policosanol	–	–

Level of evidence A: data derived from multiple randomized clinical trials or meta-analyses, B: data derived from a single randomized clinical trial or large non-randomized studies, C: consensus of opinion of the experts and/or small studies, retrospective studies, registries.

[a] Classification magnitude of effect and levels of evidence is partly adapted from ESC/EAS guidelines [12]. Magnitude of effect: + + = between 5% and 10%, + = less than 5%, - = no effect.

plant sterols and plant stanols at higher intakes. However, studies designed to answer this question are lacking and therefore conclusions regarding relative efficacy of plant sterols and plant stanols at higher intakes cannot be drawn. Plant sterol and plant stanol enriched products can lower LDL-C concentrations in different populations and are incorporated into different matrices as extensively reviewed [18,19].

Red yeast rice (RYR) is another example of a supplement with clear cholesterol-reducing properties. It is produced by the fermentation of common rice with the yeast *Monascus purpureus* mold. RYR has a hypocholesterolemic effect due to the presence of monacolin K that inhibits HMG-CoA reductase, the rate-limiting enzyme for hepatic cholesterol synthesis. In fact, monacolin K was the first statin drug (lovastatin) to be isolated and approved for treatment of high cholesterol levels [20]. Moreover, a meta-analysis of 20 RCTs with 6653 participants (follow-up between 2 months and 3.5 years) and a monacolin K dose varying from 4.8 to 24 mg per day showed that RYR supplementation lowered LDL-C levels compared with placebo (−1.02 mmol/L), while reductions were comparable when compared to standard statin therapy (pravastatin 40 mg, simvastatin 10 mg, or lovastatin 20 mg) [23]. Since the area in which RYR is produced influences the quality, it is important to note that the monacolin K content can vary [24]. In the USA, RYR is regulated as a drug, while in Europe RYR is regulated as a food supplement and can be purchased without prescription. In 2011, the European Food Safety Authority (EFSA) approved a health claim regarding the consumption of RYR as a food supplement containing monacolin K (10 mg) for the maintenance of normal blood LDL-C levels [25]. However, since monacolin K is structurally identical to lovastatin, in 2018 the EFSA recently raised safety concerns related to some side-effects commonly associated with the treatment with statins [26]. Nevertheless, an expert panel concluded recently that the use of RYR-based food supplements and nutraceuticals may play a role in reducing the global burden of cardiovascular disease and that monacolin K at 3 mg/day appears to essentially and safely reduce LDL-C levels [27].

Another dietary approach to lower serum LDL-C concentrations are soluble fibers, which are found for example in psyllium, oats and barley. Soluble fibers bind to cholesterol and bile acids in the intestinal lumen, making them unavailable for intestinal absorption and thus increasing their excretion in feces. This increased excretion will stimulate hepatic bile acid and cholesterol synthesis and, due to a reduction in free cholesterol in the liver, LDL-receptor expression will be upregulated leading to a reduction in TC and LDL-C concentrations in the circulation [28]. Soluble fibers can also undergo colonic fermentation to produce short-chain fatty acids (SCFAs). These SCFAs are rapidly taken up and transported via the portal vein directly to the liver where they are thought to inhibit endogenous cholesterol synthesis [29]. A meta-analysis of 58 RCTs with 3974 participants found that a median dose of 3.5 g/day of β-glucan can modestly reduce LDL-C concentrations (−0.19 mmol/L; −4.2%), non-HDL-C concentrations (−0.20 mmol/L; −4.8%) and apoB concentrations (0.03 g/L; −2.3%) [30]. Comparable reductions in LDL-C and non-HDL-C concentrations are found in other meta-analyses [31,32]. The cholesterol-lowering effect of soluble fiber is also supported by a health claim from the Food and Drug Administration (FDA), which states that water-soluble fiber from oat meal, when part of a diet low in saturated fat and cholesterol, may reduce the risk of coronary heart disease. They concluded that at least 3 g of β-glucan should be consumed on a daily basis to achieve an effective decrease in serum cholesterol concentrations. Although less frequently studied, the FDA also approved a claim regarding the cholesterol-lowering effect of psyllium seed husk [33]. Next to β-glucan and psyllium, another major type of soluble fibers are pectins, which are present in fruit and vegetables [34]. Even though there is no health claim regarding the cholesterol-reducing effect of pectins, foods that provide at least 6 g per day of pectins in one or more servings can claim that consumption of pectins are able to maintain normal blood cholesterol concentrations [35].

Considerable attention has also been given to the associated health benefits of soy, particularly the LDL-C lowering capacity of soy protein. In general, soybeans are a valuable source of nutrients since they contain high-quality protein, PUFAs, carbohydrates, dietary fibers, isoflavones and plant sterols. Soy protein can be consumed directly by eating soybeans and soy products or as a supplement in the form of soy protein isolate [36]. Several meta-analyses investigated the effect of soy protein or soy isoflavone intake on lipid levels, and all have found a slight hypolipidemic effect [37–39]. The cholesterol-lowering effect of soy protein is probably due to both reduced consumption of saturated fats in the diet and the effects of bioactive compounds (isoflavones) in soy itself [40]. The cholesterol-lowering effect of soy protein is documented in a health claim in Canada, stating that '*the inclusion of at least 25 g of soya protein/d as part of a diet low in saturated fat can help reduce blood cholesterol*' [41]. However, there is no health claim for soy protein and LDL-C lowering in Europe [42], and the FDA is considering to withdraw the heart health claim for soy protein due to a lack of consistent LDL-C reduction in clinical studies. As mentioned before, soybeans are also a source of isoflavones, phytosterols and lecithins, as well as soluble fibers, saponins and polysaccharides. A meta-analysis of 35 RCTs with 2670 participants (follow-up between 4 weeks and 1 year) showed a significant LDL-C reduction of −0.13 mmol/L after consumption of soy products [39]. While they did not find an effect of isoflavones, whole soy products appeared to have a stronger hypolipidaemic effect than soy supplements, which might be explained by a synergistic effect of its components. Furthermore, soy lipids such as lecithins and phospholipids could also potentiate the hypolipidemic effect of soy by inhibiting intestinal cholesterol absorption and promoting biliary cholesterol excretion [45]. Moreover, a combination of soy fibers and phospholipids with soy protein had an additive cholesterol-lowering effect compared to soy protein consumption alone [46]. Therefore, it can also be postulated that the lipid-lowering effect of whole soy products is (partly) mediated by its constituents that act in synergy with protein.

There are also other functional foods – besides the more traditional foods mentioned above – that can lower LDL-C concentrations. One of these functional foods are probiotics, which are defined as living microorganisms that, when administered in adequate amounts, can colonize the human gastrointestinal tract and confer health benefits to the host [47]. Human clinical studies yielded mixed results, most likely due to differences in experimental designs, sample size, strains and dosages of probiotics, or in subject characteristics. However, both consumption of conventional and probiotic yoghurts reduced total and LDL-C concentrations [48]. A few meta-analyses have been executed and small but statistically significant reductions in LDL-C concentrations were seen without affecting HDL-C or triglycerides concentrations [49–51]. To obtain LDL-C reducing effects, 1–2 servings of probiotic yoghurt (175–350 g) should be consumed per day to attain a minimum of 10^7 colony-forming units (CFU), which can easily be incorporated into a healthy diet [52]. *Bifidobacterium animalis* and *Lactobacillus acidophilus* are the two most commonly studied probiotic strains and most strains of probiotic bacteria possess bile salt hydrolase activity (BSH) and thus are able to deconjugate bile acids. Many hypotheses have been proposed about the mechanisms by which probiotics lower cholesterol levels and most of them are from *in vitro* experiments. The most profound probiotic cholesterol-reduction mechanism has been attributed to this BSH activity, resulting in an increased intestinal fecal excretion of cholesterol and deconjugated bile acids. As a consequence, LDL-receptor mediated LDL clearance is upregulated to produce new bile acids to compensate for the lost ones. Other possible mechanisms include their ability to absorb cholesterol themselves, to promote production of short-chain fatty acids from oligosaccharides, which can bind to PPARs and inhibit the activity of LPL and to convert cholesterol to coprostanol, which is not well absorbed [53]. Even though the effects of probiotics on LDL-C concentrations are promising, most studies are small-scale so more research is warranted.

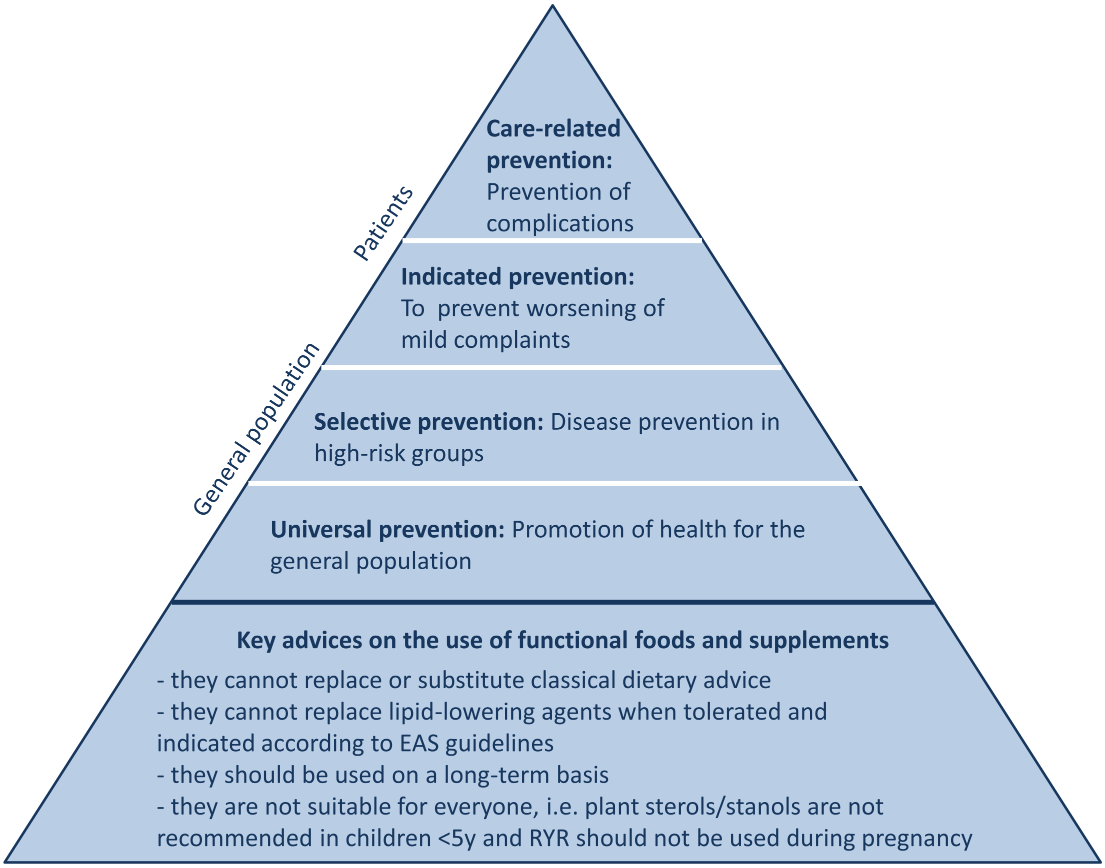

Fig. 1. The use of functional ingredients and supplements to lower LDL-C levels: target population and key advices.

Berberine, an isoquinoline plant alkaloid belonging to the class of protoberberines present in several plants such as Berberis vulgaris, Coptis chinensis, Berberis aristate, also gained interest as a potential dietary supplement to improve dyslipidemia [54]. While the majority of evidence stems from animal studies [55–57], several clinical studies also tested the efficacy of berberine in humans. In hypercholesterolemic subjects, berberine induces a significant reduction of TC, LDL-C and triglycerides levels and a significant increase of HDL-C levels, without major adverse effects [58]. In 2015, a systematic review indicated that berberine combined with oral lipid-lowering drugs reduced TC and LDL-C concentrations to a larger extent than lipid-lowering drugs alone in hyperlipidemic patients [59]. A more recent meta-analysis, 16 trials with 2147 subjects and dosages of berberine ranged from 600 mg to 1500 mg per day, concluded that berberine significantly reduced TC concentrations by −0.47 mmol/l (95% CI, −0.64 to −0.31], LDL-C concentrations by −0.38 mmol/l (95% CI, −0.53 to 0.22) and triglyceride concentrations by −0.28 mmol/l (95% CI, −0.46 to −0.10) [60]. The main mechanism by which berberine can reduce cholesterol concentrations relates to its increased effect on hepatic LDL-receptor expression and reduced expression and secretion of PCSK9 [61]. Given the limited number of well-designed clinical studies, long-term trials in large populations are warranted to establish the possible clinical beneficial effects of BBR as well as its long-term safety.

Bergamot, the common name of the fruit Citrus bergamia Risso, attracted considerable attention due to its specific flavonoid composition, since it contains some flavanones that can act as natural statins [62]. This fruit is primarily found in Southern Italy and is suggested to have antioxidant, anti-inflammatory [63], and cholesterol reducing effects [64]. The results of five different clinical trials ranging from 30 days to 6 months using bergamot in various forms indicate that the polyphenol fraction can lower TC and LDL-C concentrations, while effects on triglycerides and HDL-C concentrations are less consistent [65]. The mechanism of action for this lipid-lowering effect appears to be the inhibition of HMG-CoA reductase, however, further studies are required to confirm this proposed mechanism. Another functional food that is suggested to inhibit endogenous cholesterol biosynthesis are policosanols, which are long-chain sugar alcohol compounds extracted from sugar cane, wheat germ, rice or maize [66]. Early studies of policosanol supplementation showed reductions in both TC and LDL-C levels after policosanol consumption [67,68]. However, the results found in a series of studies performed by a Cuban group could not be confirmed by other researchers [69]. Nevertheless, policosanols are still found in many lipid-lowering supplements but the absence of independent studies raises questions regarding their efficacy to improve dyslipidemia.

Level of evidence A: data derived from multiple randomized clinical trials or meta-analyses, B: data derived from a single randomized clinical trial or large non-randomized studies, C: Consensus of opinion of the experts and/or small studies, retrospective studies, registries.

3. Functional ingredients and supplements in universal and/or care related prevention

3.1. Functional food ingredients and supplements in universal/selective prevention

The relationship between dietary factors and CVD risk was a major focus of research in the last decades. Epidemiological and clinical studies indicate that the risk of CVD is reduced by a diet rich in fruits, vegetables, unrefined grains, fish and low-fat dairy products, and low in saturated fats and sodium. Although adherence could be difficult, nutritional interventions are effective primary prevention strategies to reduce several risk factors of CVD including LDL-C concentrations [70]. Whole diet approaches, such as the Portfolio diet successfully lowered TC and LDL-C concentrations [71]. Functional ingredients and supplements can play an important role in universal and selective prevention, i.e. disease prevention in the general population and in populations at risk, such as elderly people (Fig. 1). The recent EAS/ESC guidelines for the management of dyslipidaemias emphasize that LDL-C lowering represents the primary target for reducing future CV risk. For this reason, they dedicated a full section to lifestyle recommendations on how to improve plasma lipid levels and besides certain food choices, such as the reduction of saturated fatty acids, they also include the addition of functional foods with a high level of evidence concerning their efficacy, such as plant sterols/stanols, RYR and soluble fibers [12]. These guidelines highlight that lifestyle changes are not only intended for subjects at increased CV risk, but also for the general population.

3.2. Functional food ingredients and supplements as add-on therapy to pharmacological interventions; a place in indicated/care-related prevention

Besides being used as single molecule interventions, an additional advantage that clearly needs more attention is the fact that functional foods or supplements that lower serum LDL-C concentrations might also be used in conjunction to other lipid lowering drugs as already used in the treatment of patients with elevated or high CVD risk. This approach can be regarded as indicated or care related prevention clearly focused on patient populations (Fig. 1). The limited number of studies that explored this application are extremely important since these types of observations could further optimize their clinical use by transferring the use of LDL-C lowering functional ingredients from primary or universal prevention to the clinical setting. For example, LDL-C lowering ingredients that exert their effect from inhibiting intestinal cholesterol absorption might have additive effects on top of statins, which inhibit the rate limiting enzyme in endogenous cholesterol synthesis, HMG-CoA reductase. Indeed, combining plant sterols or stanols with statin treatment shows an additional reduction in serum LDL-C concentrations of 10–15% on top of the statin effect [72–75], which confirms the dual action as explained via additive mechanisms. Interestingly, plant sterols also showed additional LDL-C lowering effects when applied on top of ezetimibe treatment [76]. This might seem, at first sight, unexpected since both ezetimibe and plant sterols inhibit intestinal cholesterol absorption, however, they apparently act via different mechanisms. The effect of plant sterols is additive to the inhibition of NPC1L1 activity via ezetimibe. Finally, although the data is less convincing, there are also indications that plant sterols act on top of fibrate treatment [77,78]. Other functional food ingredients or supplements have not been studied in combination with other LDL-C lowering pharmacological interventions in great detail [79], but need further exploration for the same reasons.

4. Advantages and limitations in the use of functional ingredients and supplements to prevent CVD

4.1. Can functional ingredients and supplements help patient's empowerment?

Long-term adherence to diet and lipid-lowering agents is a key issue. Good adherence strongly associates with LDL-C decrease and cardiovascular benefit [80]. Studies aiming to improve adherence usually translates into better lipid profiles [81,82]. For example, a lifestyle-focused text-message program improved adherence to the dietary guideline recommendations, and specifically improved self-reported consumption of vegetables, fruits, fish, takeaway foods and salt intake. Importantly, these improvements partially mediated improvements in LDL-C [81]. When considering diet and functional ingredients and supplement several aspects regarding adherence need to be considered.

First, it might be hypothesized that patients consuming functional foods rely on their significant effects on LDL-C and subsequently become less compliant with usual dietary advice. Nevertheless, an observational study demonstrated a significant change in cardiovascular-related lifestyle behaviors concomitantly with plant sterol-enriched food consumption [83]. On average, food choices improved and physical activity increased in the sample population. Although the consumption of plant sterol-enriched food has no direct effect on patient behavior as such, the concomitant improvements reported in this study may reflect underlying patient empowerment and the establishment of a virtuous circle. Patient empowerment encompasses not only patients' ability to make decisions and play an active part in their own care in line with medical advice but also includes understanding and involvement in disease prevention.

Second, it might be hypothesized that patients prescribed with statins might consequently be less adherent to both diet and functional food. This excludes RYR since it is not recommended in patients treated with statins. Furthermore, most of the patients made the choice to take RYR because of real or perceived intolerance to statin. Few studies report specific details about compliance with both diet and medication in hypercholesterolaemia. In a large survey in French patients, we found that it is the same patient who complies with both diet and medication [84]. A study conducted in 800 patients in secondary prevention showed that after one-year, overall adherence to prescribed evidence-based drugs was higher in the intervention group ($\geq$80%) than in the control group. This increase in adherence coincided with smoking cessation, regular physical activity, and healthy diet [85].

Third, considering the reported variation in response to dietary interventions, there is an emerging recognition that this should be considered in the development of personalized nutrition [86,87]. Personalized nutrition or dietary advice that has been tailored for an individual offers the possibility of improving health and reducing risk of diet-related diseases. It is tempting to encourage plant sterol intake specifically to good responders and avoid it in non-responders [88–90]. However, the effect of each individual lipid lowering food complement is within the margin of fluctuation of LDL-C (approximatively 10%). Therefore, it is difficult in practice to identify good responders. Further research is needed to identify potential good responders and to tailor recommendations depending on patient characteristics. Beyond such approach, the choice of patient is of major importance. Indeed, consumers' acceptance and preferences toward nutrition-modified and functional products may be very heterogeneous, with usually better acceptance among women and older patients [91]. Patients should be clearly informed on benefit and safety issues if they want to consume functional foods.

4.2. Costs of functional ingredients and supplements

The option to consume functional foods enriched with cholesterol-lowering ingredients is not feasible for every subject. Functional foods enriched with relatively high amounts of cholesterol-lowering ingredients are often more expensive as compared to similar non-enriched products. This is a complex but extremely relevant issue, since it is well known that the manifestation of lifestyle associated cardiovascular risk factors (so not genetic predispositions which are obviously income-independent) coincides with a lower socio-economic status [92]. Moreover, subjects in higher socio-economic classes are also more active in monitoring and controlling their risk factors [93]. This means that with an ever-growing gap between low- and high-income groups in our society, large subpopulations that theoretically might benefit most from using these products are simply not able to incorporate them in their daily dietary routines. An additional aspect related to the higher costs of these functional foods is that the extra costs are - in contrast to pharmacological agents that lower serum cholesterol concentrations - not reimbursed by health insurance companies. Here, society really misses an excellent opportunity to lower healthcare-related expenses. To illustrate this point, we here refer to two recent reports assessing the cost-effectiveness of foods with added plant sterols or stanols. The first report describes the cost-effectiveness as a primary prevention strategy for people with CVD in the UK [94], and the potential healthcare cost savings that could be derived from plant sterol/stanol intake in the European Union [95], illustrating the potential benefits on public health including health economics. The report was written by a non-profit organization upon request of Food Supplements Europe (http://www.foodsupplementseurope.org/value-of-supplementation). Total avoidable healthcare cost savings by the use of plant sterol/stanol supplements in Europe is €5.3 billion per year. After subtracting implementation costs of €1.2 billion, the annual saving in Europe is €4.1 billion. Moreover, it was calculated that the return from healthcare savings for each €1 spent on supplementation is €4.37. The second report by Yang et al. [94] described that daily intake of spreads enriched with plant sterols or stanols, assuming a 50% compliance rate, could save 69 CVD events per 10,000 men and 40 CVD events per 10,000 women aged 45–85 years over a period of 20 years. These calculated estimates illustrate that incorporating functional foods with a proven LDL-C lowering efficacy certainly make a difference in (future) health care costs. In other words, it is of utmost importance to think about inventive reimbursement strategies to collect optimal efficiency from efforts to increase the use of functional foods that lower serum cholesterol concentrations. In this context, an example from a Dutch health insurance company that introduced a reimbursement program for enriched margarines must be mentioned [96]. By sending in barcodes from the tubs, additional costs as compared to comparable margarines were reimbursed to the buyer. By these types of small gestures, financial arguments for non-adherence at least no longer stand.

Of course, there is also an alternative for situations when functional food related costs for consumers are not reimbursed. Regular plant-based foods that can be bought in every supermarket, contain ingredients that are known for their effects on lowering cholesterol absorption and as such lower serum LDL-C concentrations and CVD risk [97–99]. For example, Yokoyama et al. [99] demonstrated in their meta-analysis that consumption of vegetarian diets was associated with lower mean LDL-C concentrations (−0.6 mmol/L or −22.9 mg/dl (95%CI -27.9 to −17,9 mg/dl); $p < 0.001$) compared with consumption of omnivorous diets in observational and clinical trials. Often the compounds that are added to functional foods or used as supplements simply derived from plant (based) foods. Typical examples are not only the above-mentioned plant sterols, which are also present in vegetable oils, soy and bread, but also viscous fibers (guar gum, pectins and beta-glucans), soy protein and soy derived isoflavones. Another example of a diet in which these regular products are well presented, the so-called portfolio diets, has been proven highly effective in lowering serum LDL-C concentrations and other CVD risk parameters [100]. The advantage of this approach is that these plant-based products not only contain the functional ingredients of interest to lower serum LDL-C concentrations, but additionally also provide a whole range of compounds that possess effects beyond LDL-C lowering and, as such, might be relevant in the prevention of other lifestyle-related concerns. It needs no explanation that this approach closely links to the general dietary advices from most international societies that promote the switch from typical Western-type diets towards more plant-based diets [101–103].

4.3. Level of evidence needed to be convincing and the need for endpoint trials

As outlined above in great detail, elevated serum LDL-C concentrations associate with an increased CHD risk, and numerous studies have shown that lowering serum LDL-C concentrations reduced this risk [6,104]. Consequently, lowering LDL-C concentrations is the predominant target for cardiovascular disease management. An ever-returning question is whether the observation that a functional food is able to lower serum LDL-C concentrations is enough to conclude that this particular (functional) food lowers CVD risk. A typical example where this issue is often debated relates to the effects of foods enriched with plant sterols and stanols. As described above, there is a consensus that these foods lower serum LDL-C concentrations up to 12% at daily intakes around 2.5 g/day [105]. Despite these very consistent observations, i.e. there are over 124 well-controlled randomized studies containing over 200 strata (type of phytosterol and dose) showing a clear dose-response relationship between intake and LDL-C reductions [106], there is apparently not enough trust in serum LDL-C concentrations alone as a causal risk factor. Of course, there is the discussion around potential atherogenicity of the plant sterols themselves [18], which illustrates that reporting changes in LDL-C alone is clearly not enough to convince the entire (scientific) community. However, the EAS consensus panel concluded in 2014 that products enriched with plant sterols or stanols do lower serum LDL-C concentrations and therefore deserve a position in the dietary guidelines [105]. Similar discussions around efficacy are currently dealt with regarding the use of RYR. Although it is well established that RYR has clear hypocholesterolemic effects due to the presence of monacolins that inhibit HMG-CoA reductase, there are several points of concern regarding the ultimate benefit in terms of CVD risk management [25]. These uncertainties surrounding RYR include amongst others the composition or more specifically the content and variation in monacolin abundance, as well as concerns regarding potential effects of components other than the monacolin itself. However, despite these concerns, an expert panel recently concluded that nutraceuticals containing purified RYR may be considered in subjects with cardiovascular risk not being on the LDL-C goal, since monacolin at 3 mg/day appears to essentially and safely reduce LDL-C concentrations [27]. Both examples of plant sterols/stanols and RYR illustrate that it is difficult to simply translate consistent effects of a (functional) food (supplement) into lowering serum LDL-C concentrations towards a lower CVD risk. Functional food ingredients are often blends or mixtures of different components, which might in theory have different or even opposite effects. Therefore, the question arises on whether there is a need for endpoint trials with these functional foods or not. So far, at least for EFSA, the provided evidence was enough to substantiate claims that say that these products lower serum LDL-C concentrations, which is a known risk factor for the development of CVD. Although there might be a remaining desire for endpoint studies like in pharma, the current situation for nutritional compounds is satisfactory and probably sufficient to be on the safe side. However, another non-scientific aspect that should also be considered is the fact that endpoint studies are not only characterized by an extremely long duration and large sample size due to the relatively small effects, but we could also question whether this should be the new standard in nutritional research. When endpoint studies have been done for one or two functional ingredients, it might occur that we demand a comparable level of evidence for other nutritional compounds. This could be disastrous for innovative concepts from small sized nutrition companies that will not enter this arena given the low revenues in nutrition as compared to pharma.

5. Conclusion

Prevention of CVD can be achieved through healthy lifestyle and optimal improvements in risk factors including high levels of LDL-C. On top of dietary advice, functional foods and food supplements with proven efficacy on plasma LDL-C levels can achieve better lipid control. Adding these products to preventive strategies can be either for all subjects (universal prevention) or more focused to patients with risk factors and/or CVD (care related prevention). In Table 2, we summarized PROS and CONS for the use of these ingredients, which can be used for universal and selective prevention in the general population, as well as for indicated and care-related prevention in patient populations. Nevertheless, it must be considered that the level of evidence for functional foods is often based on their LDL-lowering effect and an ongoing discussion is whether this observation is sufficient to conclude that this particular (functional) food lowers CVD risk. In addition,

Table 2
Use of functional ingredients and supplements with proven efficacy on LDL-C levels: PROs and CONs.

PROS	CONS
Additive effect on LDL-C decrease on top of other lifestyle recommendations and on top of lipid lowering agents when used	Effect might be modest (approximatively 10% decrease of LDL-C). A study with combined functional foods/supplement should be performed to achieve larger LDL-C reductions
Good level of evidence for the effect on LDL-C	Effect on LDL-C is heterogeneous with good and poor responders
LDL-C is causal in cardiovascular disease. Any decrease is associated with a decrease in CVD events	Not RCTs with clinical outcome (as for individual components of diet)
Usually safe	Cost might be higher that statin. No reimbursement

functional foods enriched with cholesterol-lowering ingredients are often more expensive as compared to similar non-enriched products. Therefore, it is becoming more and more important to share decisions with patients to ensure proper empowerment of preventive actions and better long-term adherence to diet and lipid-lowering agents when prescribed according to the EAS/ASC recommendations.

Declaration of competing interest

The authors declared that they do not have anything to disclose regarding conflicts of interest with respect to this manuscript.

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