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Invited review

Nutraceuticals and functional foods for the control of plasma cholesterol levels. An intersociety position paper

Andrea Poli[a,*], Carlo M. Barbagallo[b], Arrigo F.G. Cicero[c], Alberto Corsini[d], Enzo Manzato[e], Bruno Trimarco[f], Franco Bernini[g], Francesco Visioli[h], Alfio Bianchi[i], Giuseppe Canzone[j], Claudio Crescini[k], Saula de Kreutzenberg[l], Nicola Ferrara[m], Marco Gambacciani[n], Andrea Ghiselli[o], Carla Lubrano[p], Giuseppe Marelli[q], Walter Marrocco[r], Vincenzo Montemurro[s], Damiano Parretti[t], Roberto Pedretti[u], Francesco Perticone[v], Roberto Stella[w], Franca Marangoni[a]

[a] NFI - Nutrition Foundation of Italy, Italy
[b] Biomedical Department of Internal Medicine and Medical Specialistics (DIBIMIS), Università di Palermo, Italy
[c] Hypertension and Atherosclerosis Research Unit, Medical and Surgical Sciences Department, Sant'Orsola-Malpighi Hospital, Università di Bologna and SINut – Italian Society of Nutraceuticals, Italy
[d] Department of Pharmacological and Biomolecular Sciences, Università degli Studi di Milano and IRCCS MultiMedica, Milano, Italy
[e] Department of Medicine (DIMED), Geriatrics Division, Università di Padova and SISA – Italian Society for the Study of Atherosclerosis, Italy
[f] Department of Advanced Biomedical Sciences, Divisions of Cardiology and Cardiothoracic Surgery, Università Federico II di Napoli and SIPREC – Italian Society for Cardiovascular Prevention, Italy
[g] Department of Food and Drug, Università di Parma, Italy
[h] Department of Molecular Medicine, Università di Padova, Italy and IMDEA-Food, Madrid, Spain
[i] ARCA – Regional Association of Outpatient Cardiologists, Italy
[j] Obstetrics and Gynecology Unit, San Cimino Hospital, Termini Imerese and SIGO – Italian Society of Ginecology and Obstetrics, Italy
[k] AOGOI – Association of Italian Hospital Obstetricians and Gynecologists, Italy
[l] Department of Medicine-DIMED, Università di Padova and SID – Italian Society of Diabetology, Italy
[m] Department of Translational Medical Sciences, Università Federico II di Napoli and SIGG – Italian Society of Gerontology and Geriatrics, Italy
[n] Department of Obstetrics and Gynecology, Università di Pisa and SIM – Italian Menopause Society, Italy
[o] CREA - Alimenti e Nutrizione, Consiglio per la ricerca in agricoltura e l'analisi dell'economia agraria and SISA – Italian Society of Food Science and Nutrition, Italy
[p] Department of Experimental Medicine, Università la Sapienza di Roma and SIE – Italian Society of Endocrinology, Italy
[q] Endocrinology and Metabolic Diseases Unit, General Hospital, Vimercate and AMD – Italian Association of Diabetologists, Italy
[r] FIMMG, Italian Federation of General Medicine Doctors and SIMPeSV – Italian Society of Preventive and Lifestyle Medicine, Italy
[s] SIC – Italian Society of Cardiology, Italy
[t] SIMG - Italian College of General Practitioners and Primary Care Professionals, Italy
[u] Department of Medicine and Cardiac Rehabilitation, Istituti Clinici Scientifici Maugeri IRCCS, Pavia and GICR-IACPR – Italian Association for Cardiovascular Prevention and Rehabilitation, Italy
[v] Department of Medical and Surgical Sciences, Università Magna Graecia di Catanzaro and SIMI – Italian Society of Internal Medicine, Italy
[w] SNaMID – National Interdisciplinary Medical Society Primary Care, Italy

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ABSTRACT

Current evidence shows that cholesterol management either reduces the likelihood of cardiovascular disease (CVD) or slows down its progression. Hence, it is important that all health professionals make appropriate use of all the available intervention strategies to control risk factors: from dietary improvement and positive lifestyle changes to the use of functional foods, food supplements, and drugs. This review examines the effect of the most frequently occurring cholesterol-lowering substances in functional foods or in supplements across Europe, namely plant sterols and stanols, monacolin K found in red yeast rice, berberine and beta-glucans. We conclude that currently available supplements and functional foods can effectively reduce plasma LDL cholesterol levels by about 5 to 25%, either alone or in combination. Suitable candidates for these products are mainly individuals at low absolute cardiovascular risk at a young age or according to classic algorithms. Of note, despite being freely available for purchase, these products should be used following shared agreement between the physician and the patient ("concordance").

* Corresponding author at: NFI – Nutrition Foundation of Italy, Viale Tunisia 38, Milan, Italy.
E-mail address: poli@nutrition-foundation.it (A. Poli).

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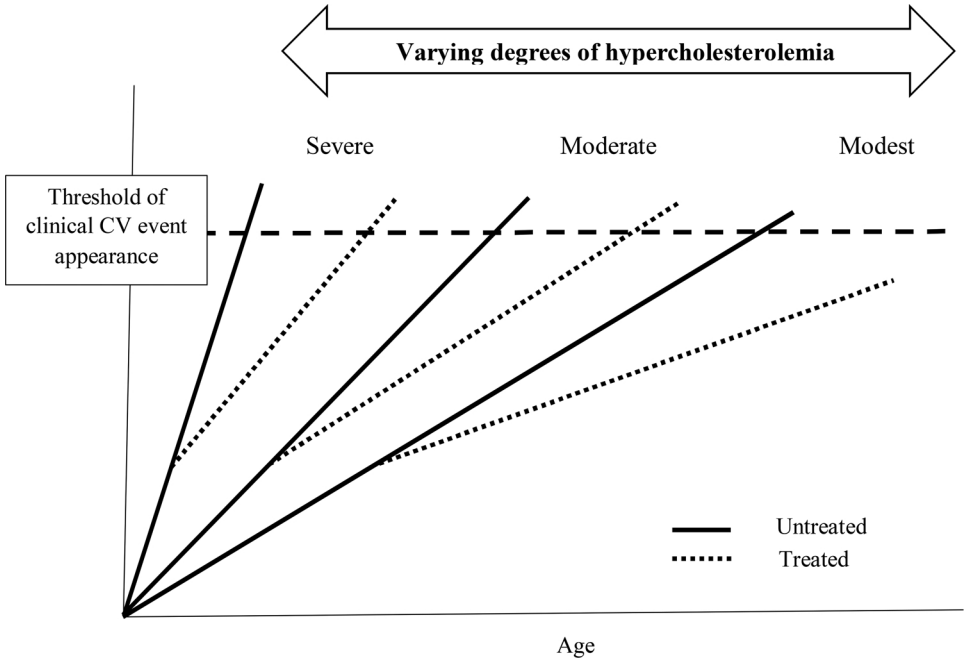

Fig. 1. Treatment effect for varying degrees of hypercholesterolemia on the potential age of appearance of atherosclerotic clinical events.

1. Introduction

All industrialised countries have observed a remarkable increase in life expectancy over the past decades. Consequently, even moderately high levels of cardiovascular risk factors are now more likely to result in clinical events given the longer duration of exposure. However, the opportunity for preventive treatment has also changed within this context; appropriate monitoring and control of risk factors, carried out in a timely and continuous manner can in fact now play an even greater role in prevention.

Current evidence confirms that such management either reduces the likelihood of cardiovascular disease (CVD) or slows down its progression (Fig. 1). It is thus crucial that all health professionals make appropriate use of all the available intervention strategies to control risk factors: from dietary improvement and adequate physical activity ("lifestyle changes") to the use of functional foods, food supplements and drugs.

2. LDL cholesterol control: an epidemiological and clinical context

There is substantial evidence to confirm that hypercholesterolemia has a direct causal relationship with atherosclerosis and related clinical events. Epidemiological studies [1], controlled intervention studies reducing plasma LDL cholesterol [2] and Mendelian randomisation studies [3] have shown that modifications of plasma LDL-cholesterol concentrations are *causally* associated with cardiovascular risk variations in the same direction and of proportional amplitude. Conversely, neither observational epidemiological studies nor Mendelian randomisations and intervention studies (even when conducted with highly efficacious drugs or drug combinations) have been able to determine a threshold value below which this direct and positive correlation between plasma LDL cholesterol levels and CVD risk is no longer detectable [4]. Lower LDL levels are hence consistently associated with a decreased risk of CVD, confirming that "the lower, the better".

Consequently, current evidence suggests that the correlation between plasma LDL cholesterol levels and risk follows an increasing monotonic curve, as opposed to the correlation between other risk factors (e.g.: hypertension, body weight and HDL cholesterol levels) and clinical events, which follows either a "J" or "U" curve [5,6]. Intervention studies using cholesterol-lowering drugs indicate that this direct correlation is reversible, in proportion to the amount of plasma LDL-cholesterol reduction and to baseline LDL-cholesterol concentrations [2,7].

Considering the monotonically increasing nature of the relationship, the causal role of LDL in the development of cardiovascular events as well as risk reversibility following treatment, it is reasonable to infer that:

- *Each reduction of plasma LDL cholesterol levels, if sufficiently extended over time, will lead to a reduction in cardiovascular risk, regardless of baseline value.* The magnitude of LDL reduction along with the length of time during which the reduction is maintained will determine the extent of risk reduction.
- Risk reduction is independent *of the specific intervention employed to reduce plasma levels of these lipoproteins*, provided that the intervention itself does not involve side effects or other unexpected responses.

3. Plasma LDL cholesterol control: the role of diet and lifestyle

Recent studies and observations have elucidated the role of diet interventions, likely overestimated in the past, in the reduction of plasma LDL cholesterol levels. Many studies have in fact found that the most commonly prescribed dietary interventions (a reduction of dietary cholesterol, saturated and *trans* unsaturated fatty acids, and an increase in polyunsaturated fatty acids) have a limited impact on LDL cholesterol levels (-1.5 - 5%) [8,9]. In addition, compliance to these dietary manipulations over time is generally low. The efficacy of dietary interventions carried out by physicians, dietitians or nurses has also been reported to be quite similar to those "self-prescribed" by the patient, thus highlighting the limited impact of such treatments [10]. Moreover, according to the most recent findings, the reduction of dietary saturated fats, albeit reducing plasma LDL cholesterol levels, does not appear to reduce either CVD risk or all-cause mortality [11]. These results question the preventive value of an intervention, which is still largely encouraged across guidelines.

On the other hand, other dietary protective effects that are not

mediated by LDL cholesterol variations may play a major role in cardiovascular prevention. An adequate intake of fibre (with metabolic and prebiotic activity), phytochemicals (especially polyphenols, which have anti-inflammatory and antioxidant properties), polyunsaturated fatty acids (anti-inflammatory, anti-thrombotic and antiarrhythmic), as examples, may contribute to reducing CVD risk and all-cause mortality, *independently of their effect on total and LDL plasma cholesterol levels* [12]. Similarly, an active lifestyle and regular aerobic physical activity are associated with a number of favourable effects on cardiovascular health, including improved vascular endothelial function, reduced oxidative stress, increased levels of plasma HDL cholesterol, weight control and especially a reduction of visceral and total body fat [11]. Consequently, such a lifestyle also leads to a significant improvement of CVD risk and overall well-being that is largely independent of the potential effects on LDL cholesterol (which are actually negligible) [13,14].

In summary, current evidence supports the idea that a healthy diet and lifestyle can reduce cardiovascular risk through mechanisms, which are largely independent of LDL cholesterol reduction. Hence, these strategies must be recommended to all patients even in the absence of clinically significant hypercholesterolemia. However, if LDL cholesterol levels are significantly above target values (for example, by 10% or more), it appears reasonable to complement diet and lifestyle (given the limited effects of these interventions alone on LDL cholesterol levels) with other interventions, focused on LDL control, from the very beginning of treatment (Fig. 2). The role of food supplements in this context deserves an evidence-based evaluation [15].

4. Active ingredients in functional foods and supplements to improve plasma LDL cholesterol levels

Until about 10 years ago, interventions aimed at reducing plasma LDL cholesterol levels were limited to dietary changes and drugs, especially statins [16]. In recent years, particularly in certain countries, there has been a surge in the use of active ingredients commonly referred to as “nutraceuticals” (formally classified as “dietary supplements” in Europe) and functional foods.

In Europe, consumers can freely purchase these products without prescription or medical advice. For this reason, patients often independently self-administer supplements and functional foods without medical input, either inappropriately or in situations in which no significant advantage can be gained.

This review will examine the effect of the most frequently occurring cholesterol-lowering substances in functional foods or in supplements across Europe, namely plant sterols and stanols, monacolin K found in red yeast rice, berberine and beta-glucans. For a more systematic overview of the pharmacology of these active ingredients, please refer to recent publications on this topic [17,18].

4.1. Plant sterols and stanols

Plant sterols and stanols (also known as phytosterols) are characterised by a polycyclic chemical structure, similar to that of cholesterol except for the side chain linked to the cyclopentane ring (D). They are present in various proportions in all plant-based products and are virtually absent in animal-based ones [19].

Phytosterols inhibit cholesterol absorption in the intestine competing for cholesterol in the formation of mixed micelles, subsequently taken up by small intestinal absorptive enterocytes via the NPC1L1 (Niemann-Pick C1-Like 1), a trans-membrane transport protein. Absorbed phytosterols are then secreted back from the enterocyte into the intestinal lumen, by specific transporters (ABCG5/G8); therefore, under physiological conditions their plasma concentration is very low [19].

Phytosterols inhibit the intestinal absorption of cholesterol, which is partly derived from foods (300–500 mg/day), and largely from the bile (1000 mg/day), in a dose-dependent way, contingent upon their total intake with food or supplements. In order to obtain a significant cholesterol-lowering effect, at least 1.5 g of phytosterols must be consumed per day. However, even a few hundred milligrams per day (especially present in Mediterranean, vegetarian and vegan diets) may have some impact on cholesterol levels [20]. The inhibition of intestinal cholesterol absorption induced by phytosterols leads to a compensatory increase of the expression of LDL receptors on the surface of hepatocytes;

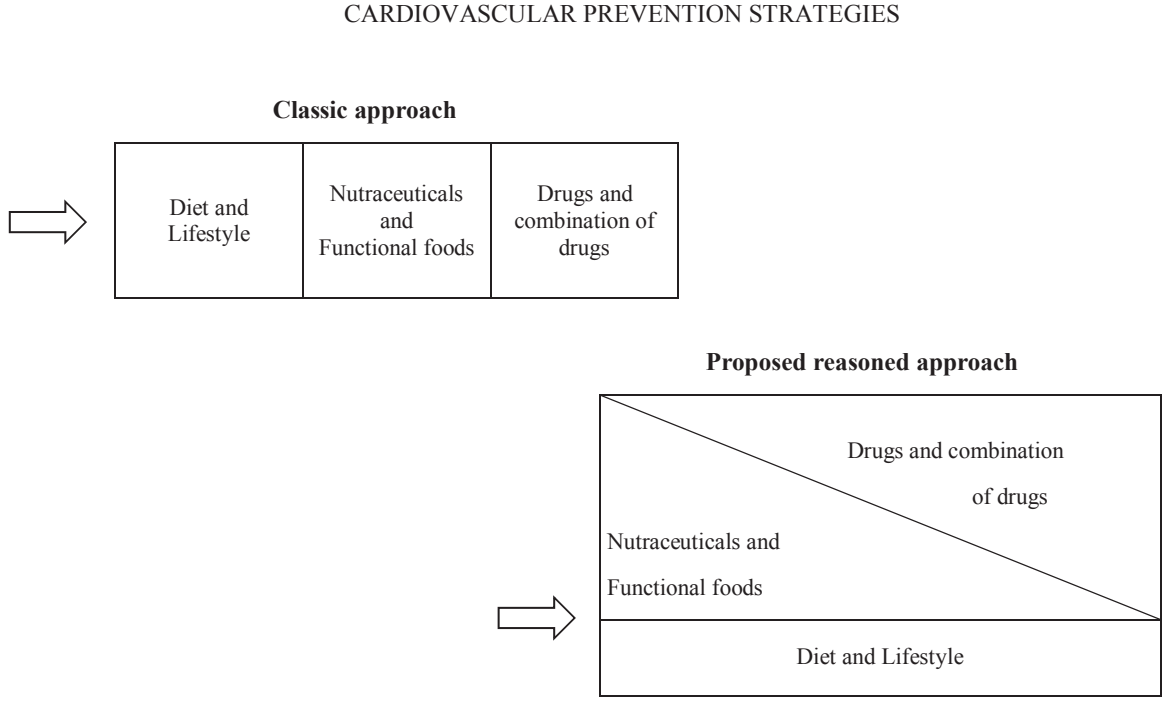

Fig. 2. Possible integration of diet and physical activity (lifestyle) interventions and the use of supplements and functional foods and drugs in cardiovascular prevention: the classic approach (left) and the proposed reasoned approach (right). NB: the figure must be read from left to right.

consequently, LDL uptake by the liver increases and their plasma concentrations are reduced [21].

Phytosterols contained in functional foods in Europe (at doses of 1.5–2.0 g/day) have been shown to reduce cholesterol by about 9–10% [22]. In contrast, plasma HDL cholesterol and triglycerides levels usually remain unaffected. The effect of phytosterols on plasma LDL cholesterol levels also leads to an improvement in vascular endothelial function, whereas their potential effect on inflammatory markers such as CRP remains controversial [23,24].

To achieve maximal efficacy, foods or supplements containing phytosterols should be taken during main meals, when cholesterol presence in the gut lumen is higher than in the fasting state due to the stimulation of biliary secretions containing cholesterol and to the dietary cholesterol derived from food [25].

Regular consumption of phytosterols can reduce the absorption of certain carotenoids and fat-soluble vitamins. It is therefore recommended to increase the consumption of such nutrients as a precautionary measure, namely by boosting the intake of brightly coloured fruits and vegetables [21].

4.2. Red yeast rice

Red Yeast Rice (RYR) derives from rice fermentation by Monascus Purpureus, or other members of the same fungal family. By fermenting rice (Oryza Sativa), these fungi produce red coloured pigments along with a group of molecules that inhibit hepatic cholesterol synthesis. Between 70 to 83% of these molecules can be identified as monacolin K, in both its lactone form (K) and the open-ring acid form (Ka). Monacolin K and Ka are easily interconverted in the body [26]. Chemically, monacolin K is identical to lovastatin and effectively inhibits HMG-CoA reductase, the rate-limiting enzyme in cholesterol synthesis. Other monacolins (J, L, X, M) found in RYR can contribute to this inhibitory process although to a much lesser extent [26,27]. Monacolins found in RYR extract are more bioavailable compared to purified lovastatin and their efficacy on cholesterol levels is consequently greater, on a mg per mg basis [28].

At doses between 3 and 10 mg/day monacolin K reduces LDL cholesterol by up to approximately 20–25%. Its effects on HDL are usually negligible, whereas triglyceridemia is reduced especially if plasma triglyceride levels are increased at baseline [29].

RYR effects in cardiovascular prevention have been confirmed in a randomised controlled trial conducted in China. RYR extracts (xuezhikang) with an average content of 2.5–3.2 mg of monacolin, administered to a population of about 5000 subjects with previous coronary events such as a myocardial infarction (China Coronary Secondary Prevention Study), led to a 20% reduction in LDL cholesterol levels, compared to placebo. The cholesterol lowering effect was associated with a significant decrease of fatal and non-fatal coronary events, stroke and all-cause mortality (-31%, -44% and -32% respectively) over the 4-year duration of the trial [30].

There is widespread belief amid the general public that RYR supplements are safer compared to statins, thus resulting in less adverse effects and a higher adhesion rate to therapy amongst patients [31]. As a result, such supplements are often considered a viable option for individuals who are intolerant to statins. It is known, however, that individuals who are truly intolerant to statins represent a minority, with most of the reported adverse effects to these drugs being explained by the “nocebo” effect [31–33]. Conclusive evidence regarding the actual safety of RYR is not available to date, however considering that monacolin K is structurally identical to a synthetically produced statin, it is reasonable to conclude that patients who are genuinely intolerant to statins should also be intolerant to RYR supplements. The higher tolerability of RYR products in individuals observed by some authors could partly be due to the low levels of the active ingredient (2.5–3 mg) that, up until recently, were found in supplements sold in Europe.

However, it should not be forgotten that monacolin K (which as previously mentioned is chemically identical to lovastatin), is metabolised by cytochrome P450 and by isoenzyme 3A4 in particular, which is involved in the metabolism of almost 30% of all drugs used in therapy [34]. Consequently, monacolin K can cause potentially significant pharmaceutical interactions: it should not be administered in conjunction with drugs containing itraconazole, ketoconazole, erythromycin, clarithromycin, telithromycin, HIV protease inhibitors, cyclosporine, nefazodone, and grapefruit juice ($\geq$0.2 L/day) [35]. Between 2002 and 2015, in fact, Italian researchers recorded 55 adverse reactions to RYR (almost all supplements contained 3 mg of monacolin during that time period) [36]. A single case of rhabdomyolisis was observed in a patient with a previous rhabdomyolisis caused by a different statin, 10 cases of liver damage were also noted as well as 19 cases of myalgia and/or CK increase, typical of statins. All observed cases returned to normal once treatment with the supplement was suspended.

Considering the widespread availability of these supplements, the absolute incidence of the related adverse side effects is rather low. Nonetheless, the importance of medical supervision for the use of supplements, especially with regards to possible interactions between RYR and other drugs, and for the selection of appropriate candidates for treatment, should not be overlooked.

Moreover, in many of the supplements recently available on the market, the amount of monacolin is now 10 mg, likely due to EFSA’s approval of the claim of “maintenance of normal cholesterol values” at this dose exclusively. The safety of monacolin at 10 mg doses as a food supplement is currently under re-evaluation by EFSA.

Due to the aforementioned reasons, combining statins with RYR based supplements is discouraged for pharmacodynamic reasons (both have the same mechanism of action) and comparable side effects.

RYR supplements are widely available online; however, it is important to select brands marketed by companies with drug-standard like industrial procedures, in order to guarantee the quality and amount of the active substance (monacolin K) and to avoid potential contamination, such as citrinin, a nephrotoxic compound found in low-quality products [27].

4.3. Beta-glucan and dietary fibre

Both dietary and supplementary intakes of fibre (i.e. complex carbohydrates that are not digested in the human gut and remain intact in the small intestine) have been proven effective in the control of plasma LDL cholesterol levels.

Fibre’s cholesterol-lowering mechanism of action is not entirely understood, although it is likely attributable to the increase of faecal excretion of cholesterol, bile acids or other dietary fats. The effect is greater for viscous soluble fibre, which absorbs water and forms a gel-like substance in the intestine [37]. Beta-glucan (a class of non-starch polysaccharides:(1→3), (1→4)-β-D-glucan) is particularly effective in this regard; this highly viscous non-digestible fibre is present in small amounts in grains and cereals and certain mushrooms and in larger amounts in barley and oats. It is also available in supplement form or as an ingredient in fortified foods [38].

Meta-analyses have quantified the magnitude of this fibre’s effect on LDL cholesterol: a daily dose of 3 g reduces LDL cholesterol by 5–6% without significantly affecting the plasma levels of other lipids [39]. Glucomannan, psyllium (a predominantly gelling polysaccharide mixture) and chitosan have also shown similar effects [18].

Beta-glucan has other favourable metabolic effects at higher doses. It positively influences glycemic levels likely due to the absorption of glucose released from digestive enzymes, subsequently slowing down its entry into the bloodstream. It also has a prebiotic effect by selectively increasing the presence of certain bacterial strains in the gut microbiota.

Table 1
Efficacy of some active ingredients on plasma LDL cholesterol.

Active ingredient	Dose	Average effect on LDL-c
Sterols and plant stanols	1.5-3.0 g/day	13.8 mg/dL (-9.2-18.3) calculated from [19]
Red Yeast Rice	3-10 mg/day (titrated in Monacolin K)	33.4 mg/dL (-27.3-39.6) [25]
Beta glucan	3.4 g/day	7,3 mg/dL (-5.4-8.8) [34]
Policosanol	10-80 mg/day	0.0 mg/dL (-13.8 + 13.8) [48]
Berberine	500-1500 mg/day	25.0 mg/dL (-20.7-29.2) [35]
Soy	30 g/day	4.8 mg/dL (-2.3-7.3) [41]

4.4. Berberine

Berberine is an alkaloid extracted from the root of the oriental Berberis plant (B. Aristata and other species). It has proven effective in controlling LDL cholesterol, which is reduced, on average, by 10–20% according to a recent meta-analysis [40]. Plasma triglycerides and HDL cholesterol levels, as well as blood glucose, are also improved [41].

Berberine possesses multiple mechanisms of action that are still undergoing investigation [42]. It appears that berberine may reduce levels of PCSK9 (Proprotein Convertase Subtilisin/Kexin Type 9) mRNA and therefore the plasma levels of this protein [43]. Berberine, on the other hand, also exerts a direct effect on LDL receptors, stabilising their encoding mRNA [44].

The combination of these two mechanisms (mRNA stabilisation and reduction of PCSK9 activity) leads to an increase in LDL receptors on the hepatic cells' surface and in cellular LDL uptake, thus decreasing LDL plasma levels. Berberine also reduces plasma triglyceride levels via opposite effects on MAP kinase (which is inhibited) and AMP kinase (enhanced). Plasma HDL cholesterol levels may increase by a few percentage points [42].

The role of berberine in glycemic control is equally as complex. The mechanism correlates with berberine's capacity to reduce the intestinal absorption and to increase the muscular and hepatic uptake of glucose. Berberine carries out an incretin like effect (increasing the release of GLP-1 and therefore of insulin) as well as an effect of insulin sensitisation [45].

Berberine has predominantly been studied in Asian subjects, its use in the Western world is relatively recent and is mainly found in products also containing RYR.

When administered *per os*, berberine's low bioavailability (2–3%) can lead to significant differences in metabolic response. Different interventions are currently underway aimed at improving its intestinal absorption. After these interventions, if effective, a new accurate safety review and evaluation of potential side effects will be required. Nowadays, berberine appears to be safe at daily intakes of 500-1,500 mg [46].

4.5. Other cholesterol-lowering elements

Over the past few years, clinical research has evaluated the cholesterol-lowering effects of many other substances. Although results remain inconclusive, they are still of interest for their possible use as nutraceuticals.

Soy derivatives (*Glycine max*) have been extensively studied in this regard. Their effects have been attributed to the content of isoflavones, lecithin and protein that promotes the expression of LDL receptors [47]. In recent years, similar observations have been made regarding the protein component of lupin [48]. Plasma total and LDL cholesterol reduction following a consumption of 25 g/day of soy protein is rather modest (4–6%) and is even less evident if baseline cholesterol levels are relatively low (around 200–220 mg/dL) [49].

Recent studies have demonstrated that many plant-derived phenolic compounds may contribute to the control of lipid profile. A meta-analysis of randomised clinical trials conducted with flavonol-based supplements established a modest yet significant reduction of plasma LDL cholesterol levels. This was evident in studies carried out in subjects with high CVD risk and in Asia, especially with quercetin, mainly found in onions, radish and fennel leaves, and apples [48,50]. Similar studies have also been conducted in Italy, with Annurca apple extracts for example [51] or with bergamot extract, in both dyslipidemic patients and subjects with metabolic syndrome [52].

The mechanism of action for polyphenols is yet to be clarified [53]. However, competitive inhibition of HMG-CoA reductase by certain HMG-type fractions (for example 3-hydroxy-3-methylglutaryl flavanone glycosides such as melitidin, brutieridin, and bergamot polyphenols [54]) has been hypothesised [55].

With regards to policosanol, a mixture of long chain aliphatic alcohols found in sugar cane and potatoes, randomised studies have reached heterogeneous conclusions. In the early 90′s, research highlighted a dose-dependent effect on cholesterol with doses between 2 and 40 mg/day. However, these findings were not confirmed by studies performed outside Cuba, and these supplements are now considered ineffective on LDL cholesterol levels [56].

Probiotics have also been suggested for the control of cholesterolemia [57]: the only available meta-analysis supporting their benefits for reducing plasma total and LDL cholesterol, especially in obese subjects with hypercholesterolemia and long-term treatments, highlights previously known criticisms regarding this complex category of nutraceuticals. The analysis of the effects of individual probiotic strains used for supplementation shows that the large majority of the strains are ineffective. Some efficacy is observed in a few studies using probiotic combinations [58].

Table 1 presents a summary of the components with plasma LDL cholesterol-lowering properties. The following summary has only considered the components for which at least one meta-analysis has been published.

4.6. Nutraceutical combinations

Some of the aforementioned molecules, with a cholesterol-lowering activity between 5 and 25% when used in monotherapy, may in theory interact if combined, thus reinforcing the effects of diets and drugs on plasma cholesterol levels [15].

In particular, the addition of berberine to supplements containing monacolin may antagonise the increased expression of PCSK9 associated with the administration of monacolin and of statins in general [59]. Similarly, phytosterols can counteract the increase in cholesterol absorption caused by statins as a compensatory mechanism [60]. These combinations can thus be useful for individuals with more marked dyslipidemia. As for all other mentioned combinations, they should exclusively be used under strict medical supervision.

It should be noted that efficacy of nutraceutical combinations on lipid profile should be supported by high quality studies, and not simply by "summing" the expected effects of individual components.

Given the multifactorial nature of atherosclerosis and the simultaneous presence of multiple risk factors in medical practice, the availability of complex supplements that are effective in the combined control of multiple risk factors is also of interest. Supplements that can simultaneously modulate plasma LDL cholesterol and blood pressure or plasma LDL cholesterol and insulin response, employing a combination of RYR, berberine and white mulberry, are currently available in Italy [61]. This second combination of effects can play a specific role in patients with metabolic syndrome, characterised by the presence of lipid abnormalities (low plasma levels of HDL cholesterol, high plasma triglyceride levels), along with increased blood pressure levels and altered glucose metabolism. It is in fact well recognised that the combination of multiple active ingredients in a single formula increases patient adhesion to therapy, reducing the number of required daily capsules, tablets or sachets [62].

It is crucial for the efficacy of ingredient combinations on various risk factors to be assessed by double-blind placebo-controlled studies. As previously noted, efficacy should *not* be inferred from the theoretical combination of the observed effects for each active ingredient.

5. Suitable candidates for the use of nutraceuticals and functional foods

In 2016, the European Society of Atherosclerosis and the European Society of Cardiology released joint guidelines for the clinical management of dyslipidemia [1]. They define nutraceutical supplementation as a pre-pharmacological intervention based on its supposed high tolerability and effects on lipid profile. However, they also underline the lack of available scientific information relating to many of these active ingredients. In the section regarding lifestyle changes, they state that low to moderate risk subjects can effectively benefit from supplementation with functional foods and nutraceuticals.

Based on the EAS/ESC guidelines, the available data proves the efficacy of RYR, plant sterols and dietary fibre while highlighting the lack of clinically significant cholesterol-lowering effect for policosanols and soy proteins, thus emphasising the need for new reliable evidence for other ingredients [1]. These guidelines also provide practical advice in order to identify patients who could potentially benefit from treatment. They suggest supplementation for patients with cholesterol levels which may be considered "borderline increased", after considering their global cardiovascular risk. Other determining criteria can be found in a recently published SISA-SID document [17].

Based on all available evidence, the choice of potential candidates for the use of nutraceuticals or functional foods in cholesterol control should follow an overall clinical evaluation of cholesterol-lowering needs, expectations regarding the risk-benefit relationship, metabolic profile, and patient specific characteristics.

As previously mentioned, it must be noted that supplementation aimed at controlling plasma LDL cholesterol levels can be initiated in parallel with diet and lifestyle interventions.

Such an approach may be considered in the following patient categories:

1 Individuals aged below 40 years, in which an algorithm like SCORE cannot be used, with no current indication for cholesterol-lowering pharmacological treatments (for example, due to the presence of familial hyperlipidemias, previous cardiovascular clinical events, or type 2 diabetes) for whom the physician, based on his/her clinical judgement, has considered reducing CVD risk via a cholesterol reduction intervention.
2 Individuals with a global CVD risk $\leq 1\%$ at 10 years, according to the SCORE algorithm, for whom the physician, based on his/her clinical judgement, has considered reducing CVD risk via a cholesterol reduction intervention.
3 Individuals with metabolic syndrome or complex metabolic disorders and a low absolute CVD risk as per the SCORE algorithm.
4 Individuals who are intolerant to statins or who are currently undergoing statin therapy with unsatisfactory outcomes (in these cases a supplement/combination of supplements free from monacolin should be considered).
5 Individuals clinically requiring a cholesterol-lowering pharmacological treatment who refuse to take statins or other ethical drugs for personal reasons or beliefs.

The use of food supplements or nutraceuticals in secondary prevention or in patients with significant vascular damage should generally be discouraged. Only a very limited number of these cases may be suitable for such use, and the caring physicians must carefully evaluate each potential patient. Even in such cases these compounds are almost always used in association with ethical drugs.

A rationale of the suggested indications is outlined below.

Individuals pertaining to points 1 and 2: results from Mendelian randomisation studies conducted on carriers of cholesterol-lowering genetic variations are of interest for these individuals. These studies found that cholesterol-lowering polymorphisms, inducing low or moderate plasma LDL reduction, reduce CVD risk just as effectively as high intensity but shorter interventions [3]. In addition, parietal damage can be observed in the "normal to high" range of values for plasma cholesterol levels that are not normally subject to lipid lowering therapy [63]. Based on the findings from published trials, it can thus be assumed that a moderate to medium reduction of plasma cholesterol levels obtained with supplements or functional foods can lead to a significant long-term risk reduction. Such an approach is scientifically sound even if treatment is initiated before patients reach a CVD risk level high enough to require specific drug therapy as defined by guidelines. A nutraceutical-based therapy for cholesterol treatment can be pursued in such conditions if patients are willing to personally fund their treatment without support from the national healthcare services and have been adequately informed by their physician (i.e. there is a well-established patient-physician agreement).

It must also be noted that the accuracy of the algorithm-based guidelines used to estimate the need for a cholesterol-lowering drug is not fully satisfactory. According to a recent study, among individuals who suffered a first myocardial infarction before 50 years of age, prior to the event a mere 30% presented a risk profile high enough to require statin use as a primary prevention strategy [64]. Therefore, in over two thirds of cases, an acute coronary event can occur in the absence of a guideline recommendation to statin prescription and use. Consequently, it appears unwarranted (or even unethical) to prevent individuals from taking responsibility for their cholesterol levels, especially if discussed with their physicians, in light of the described guideline limitations.

In the case of patients with metabolic syndrome (see point 3), a treatment that simultaneously controls multiple metabolic disturbances (plasma triglycerides and HDL cholesterol levels, glycemia) thus reducing global CVD risk, can be considered.

In selected cases (see point 4), if for whatever reason a statin is not well tolerated or not effective enough in monotherapy, the physician may either choose to suggest a monacolin-free supplement, or to add it to an insufficiently effective ongoing statin treatment. Finally, the physician may decide to consider and implement the patient's preferences, albeit they may not necessarily be rational (see point 5).

Fig. 3 illustrates a flow-chart outlining the evaluation process to determine potential suitability for nutraceutical supplement use.

After the decision to start a food supplement or a nutraceutical treatment has been made, an active ingredient or ingredient combination can be chosen based on either of the following criteria:

a "To target" approach: the physician must establish a therapeutic target for the patient. According to the EAS guidelines, given that these patients often have low CVD risk, the target is generally at or below 115 mg/dL of LDL-c. The most appropriate functional food or nutraceutical (alone or combined) to reach this target can be chosen after having determined the required magnitude of LDL reduction.
b The "lower the better" approach: in order to obtain the desired level of cholesterol reduction, the physician and the patient will choose the appropriate functional food or nutraceutical (alone or in combination).

The "to target" approach appears more suitable for group 2 and 4 patients while the "lower the better" approach is more suitable for groups 1, 3 and 5.

5.1. Specific patient populations

The rate of diabetes mellitus is steadily increasing and currently this diagnosis affects about 8% of the Italian population (type 2 diabetes covers more than 90% of these diagnoses).

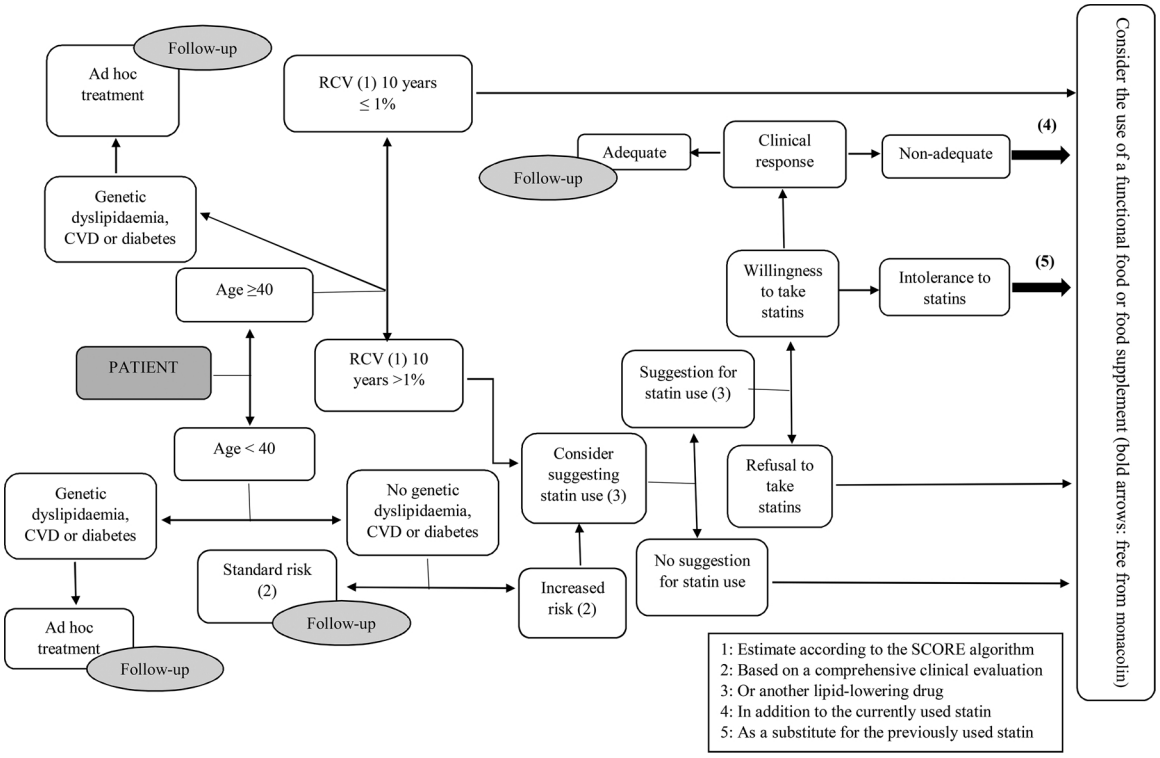

Fig. 3. Flow chart to identify potential candidates for the functional foods or nutraceutical supplements described in this document.

In diabetic patients, dyslipidemia is usually characterised by hypertriglyceridemia and low HDL cholesterol levels. Nonetheless, given that diabetic patients are at a higher risk of CVD and therefore have lower LDL targets compared to the normal population, only a fraction of them is usually "at target". In Italy, for example, only 48% of type 2 diabetics have plasma LDL cholesterol levels < 100 mg/dL, and 22% have an LDL > 130 mg/dL. The remaining 30% have an LDL value in the "grey area" between 100 and 130 mg/dL [65]. Cholesterol-lowering nutraceuticals can thus be appropriate for use in diabetics with moderate hypercholesterolemia and low cardiovascular risk. It must be noted that such patients tend to be "synthesisers", rather than "absorbers" (and therefore suited to use a monacolin supplement) [66], and that nutraceuticals including fibre, berberine and white mulberry can positively affect their triglyceride plasma levels and glucose metabolism.

According to the SCORE and other algorithms, the global CVD risk in premenopausal or initial post-menopausal women is generally low or very low. However, a recent study has found that such algorithms are limited in their ability to accurately identify women who will undergo a premature coronary event, even more so than for the general population (approximately 15 vs 30% respectively) [64]. The use of cholesterol-lowering nutraceuticals or functional foods in women during this stage of life can thus be considered based on an individual clinical evaluation, for example if a woman has a family history of CVD.

In the elderly (both male and female), special attention should be paid to cholesterol control strategies aimed at cardiovascular prevention. Observational studies suggest that the correlation between all-cause mortality and plasma cholesterol levels follows a "U" shaped curve in this population group. Frail elderly are often carriers of an "inverse metabolic syndrome", typical of this age group, characterised by low blood pressure, low body mass index, and low plasma cholesterol levels [67].

In addition, trials conducted in elderly populations looking at the possible benefits of controlling plasma cholesterol levels via statins are mainly limited to secondary prevention [68]. Conversely, given the high absolute risk in this population, preventive interventions have led to a significant reduction of clinical events and to low Number Needed to Treat (NNT). In order to decrease cardiovascular risk via cholesterol reduction, the geriatrician may carry out a clinical evaluation and consequently decide whether supplementation with functional foods or nutraceuticals is appropriate.

It is essential to consider drug interactions in this population given the high prevalence of polypharmacy.

6. The use of nutraceuticals and functional foods in the control of plasma cholesterol levels: the physician's role

The management of patients with hypercholesterolemia cannot be undertaken independently from an overall assessment of global cardiovascular risk [69]. For individuals in primary prevention, this requires the use of risk assessment algorithms. The resulting risk estimate must then be incorporated into an individualised approach. This means essentially verifying the potential presence of other risk factors such as family history for premature CVD, abdominal obesity, asymptomatic organ damage (left ventricular hypertrophy, microalbuminuria or reduced glomerular filtration rate, and atheromatous plaque in blood vessels). The presence of such conditions stratifies the risk to a higher level compared to those indicated by risk algorithms, thus leading to setting lower treatment goals.

The management and evaluation of hypercholesterolemia must be considered within the context of this anamnestic/clinical framework. The physician, preferably the one in charge of the patient's overall medical care, is responsible for this task.

The decision to recommend a functional food or supplement/nutraceutical entirely belongs to the clinical care process (for which the physician is exclusively responsible). It should therefore not be delegated to the patient or other professionals. Based on the most up-to-date knowledge, it should therefore be the physicians in charge who decide which supplement to prescribe and at which dose, as well as the appropriate check-ups and their frequency in order to monitor the safety and efficacy of treatment.

Furthermore, the physician should provide appropriate counselling

to patients in order to inform them of the importance and role of the supplement, and to assist them in consistently adhering to the treatment plan.

7. Product characterisation, efficacy demonstration and future research

When characterising, demonstrating efficacy and carrying out scientific research on functional foods and supplements for cholesterol control, several points must be considered.

Based on the available evidence that conclusively proves the causal relationship between LDL levels and cardiovascular risk, clinical studies directly demonstrating a reduction in cardiovascular events following the use of these products are not required. A demonstration of their effect on plasma LDL cholesterol levels is deemed sufficient.

However, the following data must be made available for each product:

1 Characterisation of products. Recognised differences in purity and origin between products on the market imply that each producer must regularly evaluate their starting biological media, using appropriate markers. This is especially important for products of botanical origin that may potentially be contaminated by undesired compounds (i.e. citrinin found in Red Yeast Rice based products).
2 Evidence of clinical efficacy. Each product's effects on lipid profile must be evaluated via placebo-controlled double-blind studies, administering the product at commercially available doses, for an adequate time, in sufficiently large populations with or without alterations in baseline lipid levels.
3 The effects of combining active ingredients should be evaluated via the same studies and should not be the result of a simple "addition" of effects from each individual active ingredient.

Evidence of clinical efficacy must be extended to all the considered clinical parameters (risk factors or markers) for associations aimed at controlling multiple risk factors.

In addition to demonstration of efficacy, clinical and experimental research could focus on the mechanism of action of active ingredients *in vitro*, in experimental animals or in humans where possible, for example *ex-vivo*. It should also explore potential effects on intermediate endpoints (for example endothelial function and systemic microinflammation).

Potential differences in cholesterol-lowering efficacy in subjects with specific genetic patterns may also be explored. Another topic of interest may be the interactions of functional foods and food supplements with intestinal microbiota, both as a "prebiotic" effect implying the selection of specific strains, and for the potential production of secondary active metabolites produced by the microbiota from the supplement.

8. Conclusions and recommendations by panel members

1 Currently available supplements and functional foods can effectively reduce plasma LDL cholesterol levels by about 5–25%, either alone or in combination.
2 Despite being freely available for purchase, these products should be used following shared agreement between the caring physician and the patient ("concordance"). During this preliminary stage, the physician should ensure that the patient understands the usage information related to these products as well as their characteristics and effects. Moreover, patients should consider the practicality of sustaining treatment costs over time, considering that such a treatment is often lengthy and in theory life-long.
3 Suitable candidates for these products are mainly individuals at low absolute cardiovascular risk either at a young age or according to classic algorithms (e.g. SCORE). With the patient's consent, the physician can seize the opportunity to reduce LDL cholesterol and therefore cardiovascular risk before cardiovascular risk levels, estimated through classic algorithms, are high enough to require treatment with hypolipidemic drugs.
4 In order to improve patient compliance, the physician may carefully consider the use of pre-established combinations of molecules affecting other risk factors.
5 Over time, the physician must monitor the use of these supplements, verifying their regular use, their effects on lipid profile as well as the potential occurrence of undesired side effects. The physician must reconsider the use of these supplements if the patient's level of cardiovascular risk changes significantly and should consider switching to an ethical drug if risk rises (e.g. if a clinical CV event occurs).
6 The physician's choice of product should acknowledge the supporting documentation provided by the licencing or producing company. Efficacy studies must be performed using the marketed formulas.
7 For the benefit of physicians who are mainly involved in clinical work and have difficulty accessing the literature directly, a periodic evaluation of the efficacy and safety of these products by scientific societies and experts is desirable.

Conflict of interest

All authors have undersigned a declaration regarding their potential conflicts of interest.

AP is President of NFI – Nutrition Foundation of Italy, a non profit Association partly supported by 18 large food companies, some of which are active in the market of functional foods and food supplements aimed at controlling cholesterol plasma levels. He also declares consultancies/speaking fees from MSD, Sanofi, Errekappa.

CMB declares consultancies/speaking fees from Aurora Biopharma, Piam Farmaceutici, MSD.

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References

[1] A.L. Catapano, I. Graham, G. De Backer, O. Wiklund, M.J. Chapman, H. Drexel, A.W. Hoes, C.S. Jennings, U. Landmesser, T.R. Pedersen, Z. Reiner, G. Riccardi, M.R. Taskinen, L. Tokgozoglu, W.M.M. Verschuren, C. Vlachopoulos, D.A. Wood, J.L. Zamorano, M.T. Cooney, 2016 ESC/EAS guidelines for the management of dyslipidaemias, Eur. Heart J. 37 (39) (2016) 2999–3058.
[2] J. Fulcher, R. O'Connell, M. Voysey, J. Emberson, L. Blackwell, B. Mihaylova, J. Simes, R. Collins, A. Kirby, H. Colhoun, E. Braunwald, J. La Rosa, T.R. Pedersen, A. Tonkin, B. Davis, P. Sleight, M.G. Franzosi, C. Baigent, A. Keech, Efficacy and safety of LDL-lowering therapy among men and women: meta-analysis of individual data from 174,000 participants in 27 randomised trials, Lancet 385 (9976) (2015) 1397–1405.

[3] B.A. Ference, Mendelian randomization studies: using naturally randomized genetic data to fill evidence gaps, Curr. Opin. Lipidol. 26 (6) (2015) 566–571.
[4] L. Masana, J. Girona, D. Ibarretxe, R. Rodriguez-Calvo, R. Rosales, J.C. Vallve, C. Rodriguez-Borjabad, M. Guardiola, M. Rodriguez, S. Guaita-Esteruelas, I. Oliva, N. Martinez-Micaelo, M. Heras, R. Ferre, J. Ribalta, N. Plana, Clinical and pathophysiological evidence supporting the safety of extremely low LDL levels-the zero-LDL hypothesis, J. Clin. Lipidol. 12 (2) (2018) 292–299 e3..
[5] F. Rahman, J.W. McEvoy, The J-shaped curve for blood pressure and cardiovascular disease risk: historical context and recent updates, Curr. Atheroscler. Rep. 19 (8) (2017) 34.
[6] D.T. Ko, D.A. Alter, H. Guo, M. Koh, G. Lau, P.C. Austin, G.L. Booth, W. Hogg, C.A. Jackevicius, D.S. Lee, H.C. Wijeysundera, J.T. Wilkins, J.V. Tu, High-density lipoprotein cholesterol and cause-specific mortality in individuals without previous cardiovascular conditions: the CANHEART study, J. Am. Coll. Cardiol. 68 (19) (2016) 2073–2083.
[7] E.P. Navarese, J.G. Robinson, M. Kowalewski, M. Kolodziejczak, F. Andreotti, K. Bliden, U. Tantry, J. Kubica, P. Raggi, P.A. Gurbel, Association between baseline LDL-c level and total and cardiovascular mortality after LDL-c lowering: a systematic review and meta-analysis, Jama 319 (15) (2018) 1566–1579.
[8] K. Rees, M. Dyakova, N. Wilson, K. Ward, M. Thorogood, E. Brunner, Dietary advice for reducing cardiovascular risk, Cochrane Database Syst. Rev. 12 (2013) Cd002128.
[9] E.J. Brunner, K. Rees, K. Ward, M. Burke, M. Thorogood, Dietary advice for reducing cardiovascular risk, Cochrane Database Syst. Rev. 4 (2007) Cd002128.
[10] R.L. Thompson, C.D. Summerbell, L. Hooper, J.P. Higgins, P.S. Little, D. Talbot, S. Ebrahim, Dietary advice given by a dietitian versus other health professional or self-help resources to reduce blood cholesterol, Cochrane Database Syst. Rev. 3 (2003) Cd001366.
[11] R.J. de Souza, A. Mente, A. Maroleanu, A.I. Cozma, V. Ha, T. Kishibe, E. Uleryk, P. Budylowski, H. Schunemann, J. Beyene, S.S. Anand, Intake of saturated and trans unsaturated fatty acids and risk of all cause mortality, cardiovascular disease, and type 2 diabetes: systematic review and meta-analysis of observational studies, Bmj 351 (2015) h3978.
[12] M.F. Piepoli, A.W. Hoes, S. Agewall, C. Albus, C. Brotons, A.L. Catapano, M.T. Cooney, U. Corra, B. Cosyns, C. Deaton, I. Graham, M.S. Hall, F.D.R. Hobbs, M.L. Lochen, H. Lollgen, P. Marques-Vidal, J. Perk, E. Prescott, J. Redon, D.J. Richter, N. Sattar, Y. Smulders, M. Tiberi, H.B. van der Worp, I. van Dis, W.M.M. Verschuren, S. Binno, 2016 European guidelines on cardiovascular disease prevention in clinical practice: the sixth joint task force of the European society of cardiology and other societies on cardiovascular disease prevention in clinical practice (constituted by representatives of 10 societies and by invited experts)developed with the special contribution of the European association for cardiovascular prevention & rehabilitation (EACPR), Eur. Heart J. 37 (29) (2016) 2315–2381.
[13] K.M. Huffman, V.H. Hawk, S.T. Henes, C.I. Ocampo, M.C. Orenduff, C.A. Slentz, J.L. Johnson, J.A. Houmard, G.P. Samsa, W.E. Kraus, C.W. Bales, exercise effects on lipids in persons with varying dietary patterns-does diet matter if they exercise? Responses in studies of a targeted risk reduction intervention through defined exercise I, Am. Heart J. 164 (1) (2012) 117–124.
[14] K. Shaw, H. Gennat, P. O'Rourke, C. Del Mar, Exercise for overweight or obesity, Cochrane Database Syst. Rev. 4 (2006) Cd003817.
[15] T.P. Johnston, T.A. Korolenko, M. Pirro, A. Sahebkar, Preventing cardiovascular heart disease: promising nutraceutical and non-nutraceutical treatments for cholesterol management, Pharmacol. Res. 120 (2017) 219–225.
[16] F. Cortese, M. Gesualdo, A. Cortese, S. Carbonara, F. Devito, A. Zito, G. Ricci, P. Scicchitano, M.M. Ciccone, Rosuvastatin: beyond the cholesterol-lowering effect, Pharmacol. Res. 107 (2016) 1–18.
[17] M. Pirro, C. Vetrani, C. Bianchi, M.R. Mannarino, F. Bernini, A.A. Rivellese, Joint position statement on "nutraceuticals for the treatment of hypercholesterolemia" of the Italian society of diabetology (SID) and of the Italian society for the study of arteriosclerosis (SISA), Nutr. Metab. Cardiovasc. Dis. 27 (1) (2017) 2–17.
[18] A.F.G. Cicero, A. Colletti, G. Bajraktari, O. Descamps, D.M. Djuric, M. Ezhov, Z. Fras, N. Katsiki, M. Langlois, G. Latkovskis, D.B. Panagiotakos, G. Paragh, D.P. Mikhailidis, O. Mitchenko, B. Paulweber, D. Pella, C. Pitsavos, Z. Reiner, K.K. Ray, M. Rizzo, A. Sahebkar, M.C. Serban, L.S. Sperling, P.P. Toth, D. Vinereanu, M. Vrablik, N.D. Wong, M. Banach, Lipid-lowering nutraceuticals in clinical practice: position paper from an International lipid expert panel, Nutr. Rev. 75 (9) (2017) 731–767.
[19] F. Marangoni, A. Poli, Phytosterols and cardiovascular health, Pharmacol. Res. 61 (3) (2010) 193–199.
[20] M.B. Katan, S.M. Grundy, P. Jones, M. Law, T. Miettinen, R. Paoletti, Efficacy and safety of plant stanols and sterols in the management of blood cholesterol levels, Mayo Clin. Proc. 78 (8) (2003) 965–978.
[21] H. Gylling, J. Plat, S. Turley, H.N. Ginsberg, L. Ellegard, W. Jessup, P.J. Jones, D. Lutjohann, W. Maerz, L. Masana, G. Silbernagel, B. Staels, J. Boren, A.L. Catapano, G. De Backer, J. Deanfield, O.S. Descamps, P.T. Kovanen, G. Riccardi, L. Tokgozoglu, M.J. Chapman, Plant sterols and plant stanols in the management of dyslipidaemia and prevention of cardiovascular disease, Atherosclerosis 232 (2) (2014) 346–360.
[22] R.T. Ras, J.M. Geleijnse, E.A. Trautwein, LDL-cholesterol-lowering effect of plant sterols and stanols across different dose ranges: a meta-analysis of randomised controlled studies, Br. J. Nutr. 112 (2) (2014) 214–219.
[23] V.Z. Rocha, R.T. Ras, A.C. Gagliardi, L.C. Mangili, E.A. Trautwein, R.D. Santos, Effects of phytosterols on markers of inflammation: a systematic review and meta-analysis, Atherosclerosis 248 (2016) 76–83.
[24] M. Kurano, K. Hasegawa, M. Kunimi, M. Hara, Y. Yatomi, T. Teramoto, K. Tsukamoto, Sitosterol prevents obesity-related chronic inflammation, Biochim. Biophys. Acta 1863 (2) (2018) 191–198.
[25] A.M. Doornbos, E.M. Meynen, G.S. Duchateau, H.C. van der Knaap, E.A. Trautwein, Intake occasion affects the serum cholesterol lowering of a plant sterol-enriched single-dose yoghurt drink in mildly hypercholesterolaemic subjects, Eur. J. Clin. Nutr. 60 (3) (2006) 325–333.
[26] G. Nannoni, A. Ali, F. Di Pierro, Development of a new highly standardized and granulated extract from monascus purpureus with a high content of monacolin K and KA and free of inactive secondary monacolins and citrinin, Nutrafoods 14 (2015) 197–205.
[27] R.Y. Gordon, T. Cooperman, W. Obermeyer, D.J. Becker, Marked variability of monacolin levels in commercial red yeast rice products: buyer beware!, Arch. Intern. Med. 170 (19) (2010) 1722–1727.
[28] C.H. Chen, J.C. Yang, Y.S. Uang, C.J. Lin, Improved dissolution rate and oral bioavailability of lovastatin in red yeast rice products, Int. J. Pharm. 444 (1-2) (2013) 18–24.
[29] Y. Li, L. Jiang, Z. Jia, W. Xin, S. Yang, Q. Yang, L. Wang, A meta-analysis of red yeast rice: an effective and relatively safe alternative approach for dyslipidemia, PLoS One 9 (6) (2014) e98611.
[30] P. Ye, Z.L. Lu, B.M. Du, Z. Chen, Y.F. Wu, X.H. Yu, Y.C. Zhao, Effect of xuezhikang on cardiovascular events and mortality in elderly patients with a history of myocardial infarction: a subgroup analysis of elderly subjects from the China coronary secondary prevention study, J. Am. Geriatr. Soc. 55 (7) (2007) 1015–1022.
[31] D.J. Becker, R.Y. Gordon, S.C. Halbert, B. French, P.B. Morris, D.J. Rader, Red yeast rice for dyslipidemia in statin-intolerant patients: a randomized trial, Ann. Intern. Med. 150 (12) (2009) 830–839 w147-9.
[32] E.S. Stroes, P.D. Thompson, A. Corsini, G.D. Vladutiu, F.J. Raal, K.K. Ray, M. Roden, E. Stein, L. Tokgozoglu, B.G. Nordestgaard, E. Bruckert, G. De Backer, R.M. Krauss, U. Laufs, R.D. Santos, R.A. Hegele, G.K. Hovingh, L.A. Leiter, F. Mach, W. Marz, C.B. Newman, O. Wiklund, T.A. Jacobson, A.L. Catapano, M.J. Chapman, H.N. Ginsberg, Statin-associated muscle symptoms: impact on statin therapy-European atherosclerosis society consensus panel statement on assessment, aetiology and management, Eur. Heart J. 36 (17) (2015) 1012–1022.
[33] A. Gupta, D. Thompson, A. Whitehouse, T. Collier, B. Dahlof, N. Poulter, R. Collins, P. Sever, Adverse events associated with unblinded, but not with blinded, statin therapy in the anglo-scandinavian cardiac outcomes trial-lipid-lowering Arm (ASCOT-LLA): a randomised double-blind placebo-controlled trial and its non-randomised non-blind extension phase, Lancet 389 (10088) (2017) 2473–2481.
[34] A. Corsini, S. Bellosta, R. Baetta, R. Fumagalli, R. Paoletti, F. Bernini, New insights into the pharmacodynamic and pharmacokinetic properties of statins, Pharmacol. Ther. 84 (3) (1999) 413–428.
[35] National Center for Biotechnology Information, PubChem Compound Database; CID = 53232. (Accessed 10/05 2018).
[36] G. Mazzanti, P.A. Moro, E. Raschi, R. Da Cas, F. Menniti-Ippolito, Adverse reactions to dietary supplements containing red yeast rice: assessment of cases from the Italian surveillance system, Br. J. Clin. Pharmacol. 83 (4) (2017) 894–908.
[37] X. Zhu, X. Sun, M. Wang, C. Zhang, Y. Cao, G. Mo, J. Liang, S. Zhu, Quantitative assessment of the effects of beta-glucan consumption on serum lipid profile and glucose level in hypercholesterolemic subjects, Nutr. Metab. Cardiovasc. Dis. 25 (8) (2015) 714–723.
[38] L. Cloetens, M. Ulmius, A. Johansson-Persson, B. Akesson, G. Onning, Role of dietary beta-glucans in the prevention of the metabolic syndrome, Nutr. Rev. 70 (8) (2012) 444–4458.
[39] H.V. Ho, J.L. Sievenpiper, A. Zurbau, S. Blanco Mejia, E. Jovanovski, F. Au-Yeung, A.L. Jenkins, V. Vuksan, The effect of oat beta-glucan on LDL-cholesterol, non-HDL-cholesterol and apoB for CVD risk reduction: a systematic review and meta-analysis of randomised-controlled trials, Br. J. Nutr. 116 (8) (2016) 1369–1382.
[40] H. Dong, Y. Zhao, L. Zhao, F. Lu, The effects of berberine on blood lipids: a systemic review and meta-analysis of randomized controlled trials, Planta Med. 79 (6) (2013) 437–446.
[41] W. Kong, J. Wei, P. Abidi, M. Lin, S. Inaba, C. Li, Y. Wang, Z. Wang, S. Si, H. Pan, S. Wang, J. Wu, Y. Wang, Z. Li, J. Liu, J.D. Jiang, Berberine is a novel cholesterol-lowering drug working through a unique mechanism distinct from statins, Nat. Med. 10 (12) (2004) 1344–1351.
[42] A. Pirillo, A.L. Catapano, Berberine, a plant alkaloid with lipid- and glucose-lowering properties: from in vitro evidence to clinical studies, Atherosclerosis 243 (2) (2015) 449–461.
[43] A.A. Momtazi, M. Banach, M. Pirro, N. Katsiki, A. Sahebkar, Regulation of PCSK9 by nutraceuticals, Pharmacol. Res. 120 (2017) 157–169.
[44] J. Cameron, T. Ranheim, M.A. Kulseth, T.P. Leren, K.E. Berge, Berberine decreases PCSK9 expression in HepG2 cells, Atherosclerosis 201 (2) (2008) 266–273.
[45] C. Liu, Z. Wang, Y. Song, D. Wu, X. Zheng, P. Li, J. Jin, N. Xu, L. Li, Effects of berberine on amelioration of hyperglycemia and oxidative stress in high glucose and high fat diet-induced diabetic hamsters in vivo, Biomed. Res. Int. 2015 (2015) 313808.
[46] C. Caliceti, P. Franco, S. Spinozzi, A. Roda, A.F. Cicero, Berberine: new insights from pharmacological aspects to clinical evidences in the management of metabolic disorders, Curr. Med. Chem. 23 (14) (2016) 1460–1476.
[47] O.A. Tokede, T.A. Onabanjo, A. Yansane, J.M. Gaziano, L. Djousse, Soya products and serum lipids: a meta-analysis of randomised controlled trials, Br. J. Nutr. 114 (6) (2015) 831–843.
[48] M. Bahr, A. Fechner, J. Kramer, M. Kiehntopf, G. Jahreis, Lupin protein positively affects plasma LDL cholesterol and LDL:HDL cholesterol ratio in hypercholesterolemic adults after four weeks of supplementation: a randomized, controlled crossover study, Nutr. J. 12 (2013) 107.
[49] J.W. Anderson, B.M. Johnstone, M.E. Cook-Newell, Meta-analysis of the effects of

soy protein intake on serum lipids, N. Engl. J. Med. 333 (5) (1995) 276–282.
[50] A. Sahebkar, Effects of quercetin supplementation on lipid profile: a systematic review and meta-analysis of randomized controlled trials, Crit. Rev. Food Sci. Nutr. 57 (4) (2017) 666–676.
[51] G.C. Tenore, D. Caruso, G. Buonomo, M. D'Avino, P. Campiglia, L. Marinelli, E. Novellino, A healthy balance of plasma cholesterol by a novel annurca apple-based nutraceutical formulation: results of a randomized trial, J. Med. Food 20 (3) (2017) 288–300.
[52] R.V. Giglio, A.M. Patti, D. Nikolic, G. Li Volti, K. Al-Rasadi, N. Katsiki, D.P. Mikhailidis, G. Montalto, E. Ivanova, A.N. Orekhov, M. Rizzo, The effect of bergamot on dyslipidemia, Phytomedicine 23 (11) (2016) 1175–1181.
[53] J. Tome-Carneiro, F. Visioli, Polyphenol-based nutraceuticals for the prevention and treatment of cardiovascular disease: review of human evidence, Phytomedicine 23 (11) (2016) 1145–1174.
[54] E. Janda, A. Lascala, C. Martino, S. Ragusa, S. Nucera, R. Walker, S. Gratteri, V. Mollace, Molecular mechanisms of lipid- and glucose-lowering activities of bergamot flavonoids, PharmaNutrition 4 (2016) S8–S18.
[55] M. Leopoldini, N. Malaj, M. Toscano, G. Sindona, N. Russo, On the inhibitor effects of bergamot juice flavonoids binding to the 3-hydroxy-3-methylglutaryl-CoA reductase (HMGR) enzyme, J. Agric. Food Chem. 58 (19) (2010) 10768–10773.
[56] J. Gong, X. Qin, F. Yuan, M. Hu, G. Chen, K. Fang, D. Wang, S. Jiang, J. Li, Y. Zhao, Z. Huang, H. Dong, F. Lu, Efficacy and safety of sugarcane policosanol on dyslipidemia: a meta-analysis of randomized controlled trials, Mol. Nutr. Food Res. 62 (1) (2018).
[57] M.P. Cavalcanti Neto, J.S. Aquino, L.F. Romao da Silva, R. de Oliveira Silva, K.S.L. Guimaraes, Y. de Oliveira, E.L. de Souza, M. Magnani, H. Vidal, J.L. de Brito Alves, Gut microbiota and probiotics intervention: a potential therapeutic target for management of cardiometabolic disorders and chronic kidney disease? Pharmacol. Res. 130 (2018) 152–163.
[58] M. Shimizu, M. Hashiguchi, T. Shiga, H.O. Tamura, M. Mochizuki, Meta-analysis: effects of probiotic supplementation on lipid profiles in Normal to mildly hypercholesterolemic individuals, PLoS One 10 (10) (2015) e0139795.
[59] T. Nozue, Lipid lowering therapy and circulating PCSK9 concentration, J. Atheroscler. Thromb. 24 (9) (2017) 895–907.
[60] T.A. Miettinen, H. Gylling, Synthesis and absorption markers of cholesterol in serum and lipoproteins during a large dose of statin treatment, Eur. J. Clin. Invest. 33 (11) (2003) 976–982.
[61] V. Trimarco, A. Battistoni, G. Tocci, R. Coluccia, M.V. Manzi, R. Izzo, M. Volpe, Single blind, multicentre, randomized, controlled trial testing the effects of a novel nutraceutical compound on plasma lipid and cardiovascular risk factors: results of the interim analysis, Nutr. Metab. Cardiovasc. Dis. 27 (10) (2017) 850–857.
[62] F. Napolitano, P. Napolitano, I.F. Angelillo, Medication adherence among patients with chronic conditions in Italy, Eur. J. Public Health 26 (1) (2016) 48–52.
[63] L. Fernandez-Friera, V. Fuster, B. Lopez-Melgar, B. Oliva, J.M. Garcia-Ruiz, J. Mendiguren, H. Bueno, S. Pocock, B. Ibanez, A. Fernandez-Ortiz, J. Sanz, Normal LDL-cholesterol levels are associated with subclinical atherosclerosis in the absence of risk factors, J. Am. Coll. Cardiol. 70 (24) (2017) 2979–2991.
[64] A. Singh, B.L. Collins, A. Gupta, A. Fatima, A. Qamar, D. Biery, J. Baez, M. Cawley, J. Klein, J. Hainer, J. Plutzky, C.P. Cannon, K. Nasir, M.F. Di Carli, D.L. Bhatt, R. Blankstein, Cardiovascular risk and statin eligibility of Young adults after an MI: partners YOUNG-MI registry, J. Am. Coll. Cardiol. 71 (3) (2018) 292–302.
[65] A.D.I. Fondazione, Annali AMD, (2012).
[66] E.M. Ooi, T.W. Ng, D.C. Chan, G.F. Watts, Plasma markers of cholesterol homeostasis in metabolic syndrome subjects with or without type-2 diabetes, Diabetes Res. Clin. Pract. 85 (3) (2009) 310–316.
[67] U.M. Vischer, M.E. Safar, H. Safar, P. Iaria, K. Le Dudal, O. Henry, F.R. Herrmann, P. Ducimetiere, J. Blacher, Cardiometabolic determinants of mortality in a geriatric population: is there a "reverse metabolic syndrome"? Diabetes Metab. 35 (2) (2009) 108–114.
[68] P. Deedwania, P.H. Stone, C.N. Bairey Merz, J. Cosin-Aguilar, N. Koylan, D. Luo, P. Ouyang, R. Piotrowicz, K. Schenck-Gustafsson, P. Sellier, J.H. Stein, P.L. Thompson, D. Tzivoni, Effects of intensive versus moderate lipid-lowering therapy on myocardial ischemia in older patients with coronary heart disease: results of the study assessing goals in the elderly (SAGE), Circulation 115 (6) (2007) 700–707.
[69] S. Khedkar, L. Carraresi, S. Bröring, Food or pharmaceuticals? Consumers' perception of health-related borderline products, PharmaNutrition 5 (4) (2017) 133–140.