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

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1 **Nutraceuticals and functional foods for the control of plasma cholesterol levels.**
2 **An Intersociety position paper.**

3

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67 Running title:

68 Functional food and nutraceuticals in plasma cholesterol control

69 **Abstract**

70

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

85

86 Key words: **Food supplements, functional food, cholesterol, LDL cholesterol,**
87 **cardiovascular risk, primary prevention**

88 **1. Introduction**

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

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

101

102 **2. LDL cholesterol control: an epidemiological and clinical context**

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

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

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

- 125
- 126 • *Each reduction of plasma LDL cholesterol levels, if sufficiently extended over*
127 *time, will lead to a reduction in cardiovascular risk, regardless of baseline value.*
128 The magnitude of LDL reduction along with the length of time during which the
reduction is maintained will determine the extent of risk reduction.
 - 129 • Risk reduction is independent of the specific intervention employed to reduce
130 plasma levels of these lipoproteins, provided that the intervention itself does
131 not involve side effects or other unexpected responses.

132

133

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

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

147 On the other hand, other dietary protective effects that are not mediated by LDL
148 cholesterol variations may play a major role in cardiovascular prevention. An adequate
149 intake of fibre (with metabolic and prebiotic activity), phytochemicals (especially
150 polyphenols, which have anti-inflammatory and antioxidant properties),
151 polyunsaturated fatty acids (anti-inflammatory, anti-thrombotic and antiarrhythmic), as
152 examples, may contribute to reducing CVD risk and all-cause mortality, *independently*
153 *of their effect on total and LDL plasma cholesterol levels* [12]. Similarly, an active
154 lifestyle and regular aerobic physical activity are associated with a number of
155 favourable effects on cardiovascular health, including improved vascular endothelial
156 function, reduced oxidative stress, increased levels of plasma HDL cholesterol, weight
157 control and especially a reduction of visceral and total body fat [11]. Consequently,
158 such a lifestyle also leads to a significant improvement of CVD risk and overall well-
159 being that is largely independent of the potential effects on LDL cholesterol (which is
160 actually negligible) [13, 14].

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

170

171 4. Active ingredients in functional foods and supplements to improve 172 plasma LDL cholesterol levels

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

178 In Europe, consumers can freely purchase these products without prescription or
179 medical advice. For this reason, patients often independently self-administer

180 supplements and functional foods without medical input, either inappropriately or in
181 situations in which no significant advantage can be gained.

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

187 *4.1 Plant sterols and stanols*

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

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

198 Phytosterols inhibit the intestinal absorption of cholesterol, which is partly derived from
199 foods (300-500 mg/day), and largely from the bile (1000 mg/day), in a dose-dependent
200 way, contingent upon their total intake with food or supplements. In order to obtain a
201 significant cholesterol-lowering effect, at least 1.5 g of phytosterols must be consumed
202 per day. However, even a few hundred milligrams per day (especially present in
203 Mediterranean, vegetarian and vegan diets) may have some impact on cholesterol
204 levels [20]. The inhibition of intestinal cholesterol absorption induced by phytosterols
205 leads to a compensatory increase of the expression of LDL receptors on the surface
206 of hepatocytes; consequently, LDL uptake by the liver increases and their plasma
207 concentrations are reduced [21].

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

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

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

222 *4.2 Red Yeast Rice*

223 Red Yeast Rice (RYR) derives from rice fermentation by *Monascus Purpureus*, or
224 other members of the same fungal family. By fermenting rice (*Oryza Sativa*), these
225 fungi produce red coloured pigments along with a group of molecules that inhibit

226 hepatic cholesterol synthesis. Between 70 to 83% of these molecules can be identified
227 as monacolin K, in both its lactone form (K) and the open-ring acid form (Ka).
228 Monacolin K and Ka are easily interconverted in the body [26]. Chemically, monacolin
229 K is identical to lovastatin and effectively inhibits HMG-CoA reductase, the rate-limiting
230 enzyme in cholesterol synthesis. Other monacolins (J, L, X, M) found in RYR can
231 contribute to this inhibitory process although to a much lesser extent [26, 27].
232 Monacolins found in RYR extract are more bioavailable compared to purified lovastatin
233 and their efficacy on cholesterol levels is consequently greater, on a mg per mg basis
234 [28].

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

239 RYR effects in cardiovascular prevention have been confirmed in a randomized
240 controlled trial conducted in China. RYR extracts (xuezhikang) with an average
241 content of 2.5-3.2 mg of monacolin, administered to a population of about 5,000
242 subjects with previous coronary events such as a myocardial infarction (China
243 Coronary Secondary Prevention Study), led to a 20% reduction in LDL cholesterol
244 levels, compared to placebo. The cholesterol lowering effect was associated with a
245 significant decrease of fatal and non-fatal coronary events, stroke and all-cause
246 mortality (-31%, -44% and -32% respectively) over the 4-year duration of the trial [30].

247 There is widespread belief amid the general public that RYR supplements are safer
248 compared to statins, thus resulting in less adverse effects and a higher adherence rate
249 to therapy amongst patients [31]. As a result, such supplements are often considered
250 a viable option for individuals who are intolerant to statins. It is known, however, that
251 individuals who are truly intolerant to statins represent a minority, with most of the
252 reported adverse effects to these drugs being explained by the “nocebo” effect [31-
253 33]. Conclusive evidence regarding the actual safety of RYR is not available to date,
254 however considering that monacolin K is structurally identical to a synthetically
255 produced statins, it is reasonable to conclude that patients who are genuinely
256 intolerant to statins should also be intolerant to RYR supplements. The higher
257 tolerability of RYR products in individuals observed by some authors could partly be
258 due to the low levels of the active ingredient (2.5 - 3mg) that, up until recently, were
259 found in supplements sold in Europe.

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

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

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

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

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

291 *4.3 Beta-glucan and dietary fibre*

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

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

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

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

312 *4.4 Berberine*

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

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

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

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

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

336 When administered *per os*, berberine's low bioavailability (2-3%) can lead to
337 significant differences in metabolic response. Different interventions are currently
338 underway aimed at improving its intestinal absorption. After these interventions, if
339 effective, a new accurate safety review and evaluation of potential side effects will be
340 required. Nowadays, berberine appears to be safe for daily intakes of 500-1,500 mg
341 [46].

342 *4.5 Other cholesterol-lowering elements*

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

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

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

361 The mechanism of action for polyphenols is yet to be clarified [53]. However,
362 competitive inhibition of HMG-CoA reductase by certain HMG-type fractions (for

363 example 3-hydroxy-3-methylglutaryl flavanone glycosides such as melitidin,
364 brutieridin, and bergamot polyphenols [54]) has been hypothesized [55].

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

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

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

381

382 *4.6 Nutraceutical combinations*

383 Some of the aforementioned molecules, with a cholesterol-lowering activity between
384 5 and 25% when used in monotherapy, may in theory interact if combined, thus
385 reinforcing the effects of diets and drugs on plasma cholesterol levels [15].

386 In particular, the addition of berberine to supplements containing monacolin may
387 antagonise the increased expression of PCSK9 associated with the administration of
388 monacolin and of statins in general [59]. Similarly, phytosterols can counteract the
389 increase in cholesterol absorption caused by statins as a compensatory mechanism
390 [60]. These combinations can thus be useful for individuals with more marked
391 dyslipidemia. As for all other mentioned combinations, they should exclusively be used
392 under strict medical supervision.

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

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

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

412

413 **5. Suitable candidates for the use of these products**

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

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

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

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

438 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.

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

444 A rationale of the suggested indications is outlined below.

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

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

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

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

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

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

483 a. “To target” approach: the physician must establish a therapeutic target for the
484 patient. According to the EAS guidelines, given that these patients often have low
485 CVD risk, the target is generally at or below 115 mg/dL of LDL-c. The most
486 appropriate functional food or nutraceutical (alone or combined) to reach this target
487 can be chosen after having determined the required magnitude of LDL reduction.

488 b. The “lower the better” approach: in order to obtain the desired level of cholesterol
489 reduction, the physician and the patient will choose the appropriate functional food
490 or nutraceutical (alone or in combination).

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

493

494 *5.1 Specific patient populations*

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

498 In diabetic patients, dyslipidemia is usually characterised by hypertriglyceridemia and
499 low HDL cholesterol levels. Nonetheless, given that diabetic patients are at a higher
500 risk of CVD and therefore have lower LDL targets compared to the normal population,
501 only a fraction of them is usually “at target”. In Italy, for example, only 48% of type 2
502 diabetics have plasma LDL cholesterol levels <100 mg/dL, and 22% have an LDL >
503 130 mg/dL. The remaining 30% have an LDL value in the “grey area” between 100
504 and 130 mg/dL [65]. Cholesterol-lowering nutraceuticals can thus be appropriate for
505 use in diabetics with moderate hypercholesterolemia and low cardiovascular risk. It
506 must be noted that such patients tend to be “synthesisers”, rather than “absorbers”
507 (and therefore suited to use a monacolin supplement) [66], and that nutraceuticals
508 including fibre, berberine and white mulberry can positively affect their triglyceride
509 plasma levels and glucose metabolism.

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

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

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

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

533

534 **6. The use of nutraceuticals in the control of plasma cholesterol levels: the** 535 **physician's role**

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

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

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

555 Furthermore, the physician should provide appropriate counselling to patients in order
556 to inform them of the importance and role of the supplement and to assist them in
557 consistently adhering to the treatment plan.

558

559 **7. Product characterisation, efficacy demonstration and future research**

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

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

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

568 1. Characterisation of products. Recognized differences in purity and origin
569 between products on the market imply that each producer must regularly
570 evaluate their starting biological media, using appropriate markers. This is
571 especially important for products of botanical origin that may potentially be
572 contaminated by undesired compounds (i.e. citrinin found in Red Yeast Rice
573 based products).

574 2. Evidence of clinical efficacy. Each product's effects on lipid profile must be
575 evaluated via placebo-controlled double-blind studies, administering the
576 product at commercially available doses, for an adequate time, in sufficiently
577 large populations with or without alterations in baseline lipid levels.

578 3. The effects of combining active ingredients should be evaluated via the same
579 studies and should not be the result of a simple "addition" of effects from each
580 individual active ingredient.

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

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

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

593

8. Conclusions and recommendations by panel members

1. Currently available supplements and functional foods can effectively reduce plasma LDL cholesterol levels by about 5 to 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 their practical possibility to sustain treatment costs over time, considering that such treatment is often lengthy and in theory life-long.
3. Suitable candidates for these products are mainly individuals at low absolute cardiovascular risk 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 classical 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.

594

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600

601

602 **Conflict of Interest**

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

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

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

611 ACicero declares consultancy for MEDA spa

612 ACorsini declares consultancies/speaking fees from MSD, Novartis, Recordati,
613 Roche, Amgen, Mediolanum, Mylan, DOC

614 BT declares consultancies/speaking fees from MSD, Daiichi

615 FV declares consultancies/speaking fees from Indena

616 RP declares consultancies/speaking fees from Menarini, Novartis, Bristol-Myers
617 Squibb, Pfizer, IBSA

618 NF declares consultancies/speaking fees from Daiichi/Sankio, NFI

619 FM is Director of Research of NFI – Nutrition Foundation of Italy, a non profit
620 Association partly supported by 18 large food companies, some of which are active in
621 the market of functional foods and food supplements aimed at controlling cholesterol
622 plasma levels.

623 Other authors declared no conflict of interest relative to this paper

624

625 **Figure Legends**

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

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

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

634

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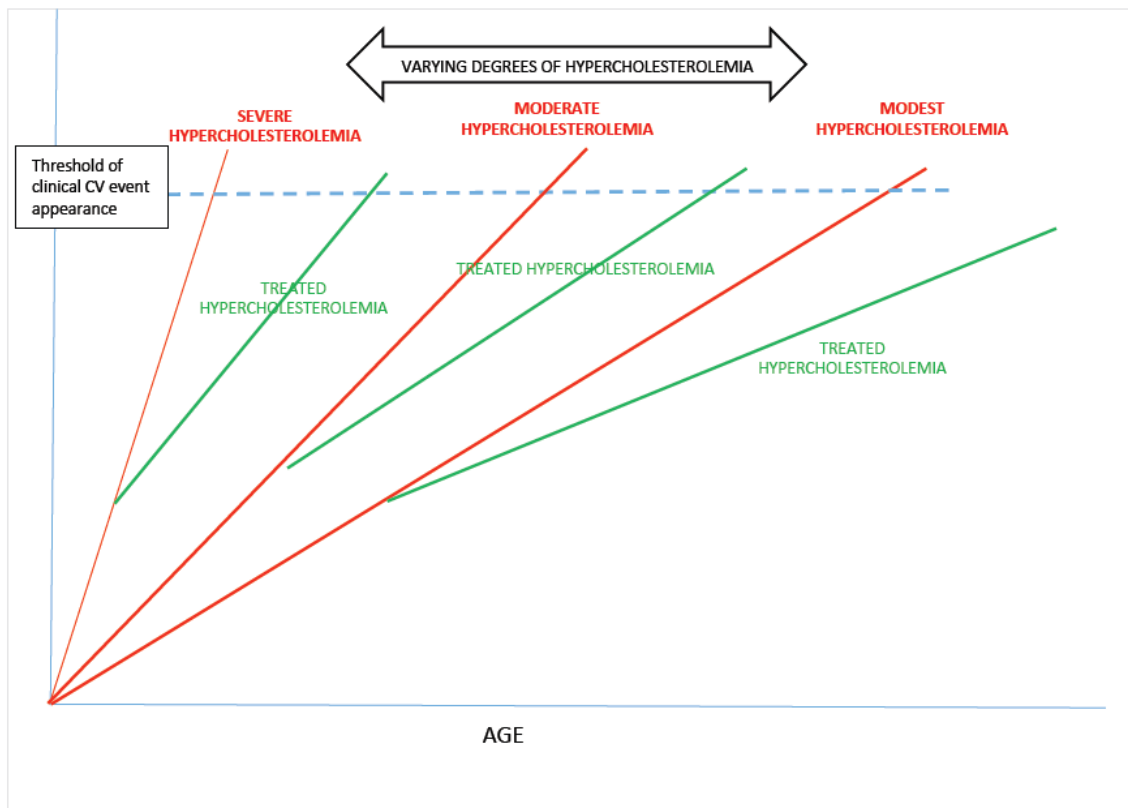
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884 Table 1. Efficacy of some active ingredients on plasma LDL cholesterol

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]

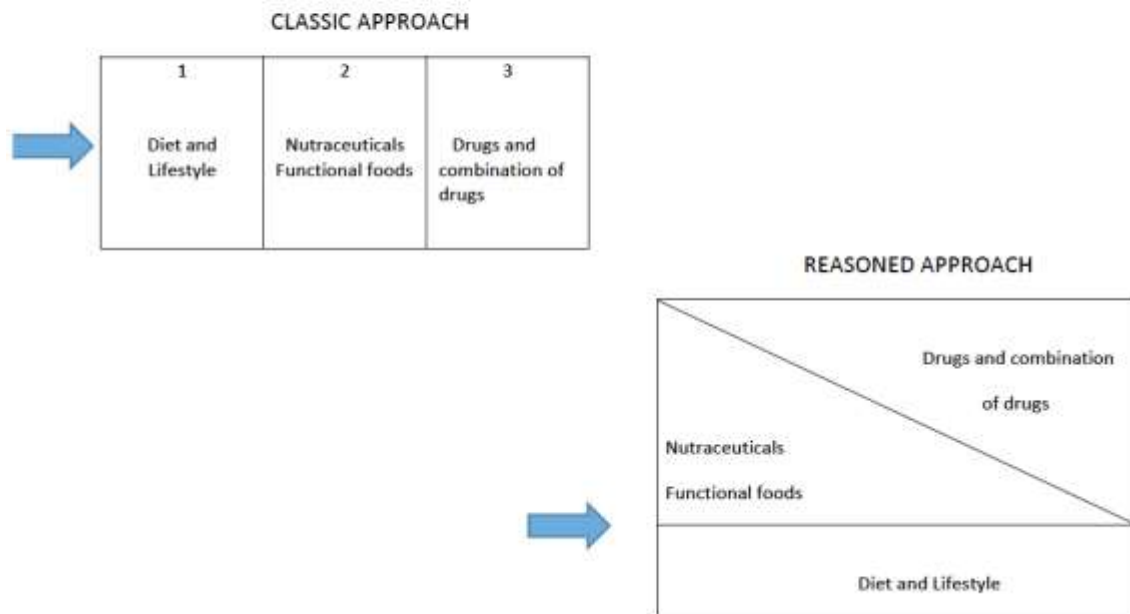
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 888 Figure 1. Treatment effect for varying degrees of hypercholesterolemia on the
 889 potential age of appearance of atherosclerotic clinical events.
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CARDIOVASCULAR PREVENTION STRATEGIES



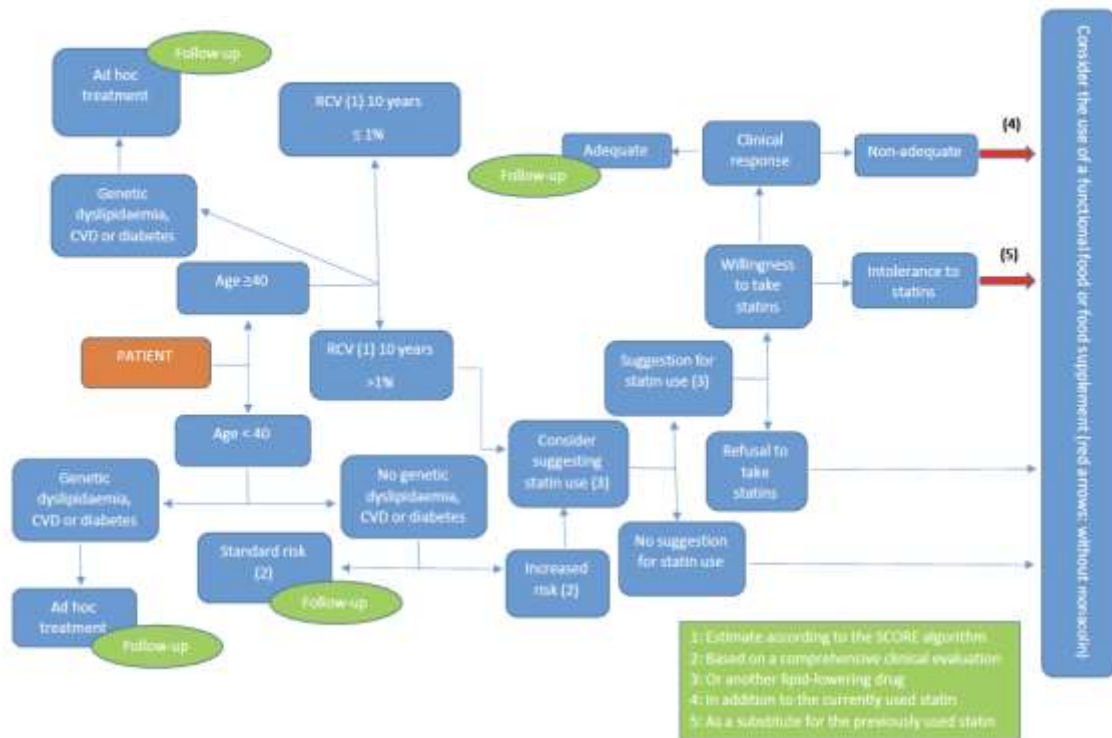
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892 Fig. 2: Possible integration of diet and physical activity (lifestyle) interventions
893 and the use of supplements and functional foods and drugs in cardiovascular
894 prevention: the classical approach (left) and the proposed reasoned approach
895 (right)

896 NB: the figure must be read from left to right (arrows)

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

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