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)

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Abstract: Hypercholesterolemia is a major risk factor for cardiovascular morbidity and mortality. There is a large body of evidence showing that low-density lipoprotein (LDL) cholesterol-lowering is associated with a significant cardiovascular risk reduction, both in primary and secondary prevention.
Treatment strategies to achieve optimal LDL cholesterol levels include both interventions on lifestyle and pharmacological measures. The initial therapeutic approach to patients with hypercholesterolemia includes a low dietary intake of cholesterol, saturated and "trans" fats and an increase in dietary fiber, associated with physical activity. However, patients compliance to these recommendations is often inadequate, especially in the medium to long term. Some dietary components with potential cholesterol-lowering activity are present in small amounts in food. Therefore, in recent years the use of "nutraceuticals" (i.e., nutrients and/or bioactive compounds with potential beneficial effects on human health) has become widespread. Such substances may be added to foods and beverages, or taken in the form of dietary supplements (liquid preparations, tablets, capsules).
A growing number of nutraceuticals with slight to moderate cholesterol-lowering activity have been proposed. However, scientific research regarding the cholesterol-lowering effect of some nutraceuticals has produced conflicting results; in addition, methodological limitations flawed the quality of several trials.
In the present document, the cholesterol-lowering activity of some nutraceuticals (i.e. fiber, phytosterols, soy products, policosanol, red yeast rice and berberine) will be discussed along with: 1) the level of evidence on the cholesterol-lowering efficacy emerging from interventional studies in humans; 2) the possible side effects associated with their use; 3) the categories of patients who could benefit from their use.

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)

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Summary

Hypercholesterolemia is a major risk factor for cardiovascular morbidity and mortality. There is a large body of evidence showing that low-density lipoprotein (LDL) cholesterol-lowering is associated with a significant cardiovascular risk reduction, both in primary and secondary prevention.

Treatment strategies to achieve optimal LDL cholesterol levels include both interventions on lifestyle and pharmacological measures. The initial therapeutic approach to patients with hypercholesterolemia includes a low dietary intake of cholesterol, saturated and "trans" fats and an increase in dietary fiber, associated with physical activity. However, patients compliance to these recommendations is often inadequate, especially in the medium to long term. Some dietary components with potential cholesterol-lowering activity are present in small amounts in food. Therefore, in recent years the use of "nutraceuticals" (i.e., nutrients and/or bioactive compounds with potential beneficial effects on human health) has become widespread. Such substances may be added to foods and beverages, or taken in the form of dietary supplements (liquid preparations, tablets, capsules).

A growing number of nutraceuticals with slight to moderate cholesterol-lowering activity have been proposed. However, scientific research regarding the cholesterol-lowering effect of some nutraceuticals has produced conflicting results; in addition, methodological limitations flawed the quality of several trials.

In the present document, the cholesterol-lowering activity of some nutraceuticals (i.e. fiber, phytosterols, soy products, policosanol, red yeast rice and berberine) will be discussed along with: 1) the level of evidence on the cholesterol-lowering efficacy emerging from interventional studies in humans; 2) the possible side effects associated with their use; 3) the categories of patients who could benefit from their use.

Key words: berberine, cardiovascular risk, cholesterol, fiber, nutraceuticals, phytosterols, policosanol, red yeast rice, soy.

Introduction

High plasma cholesterol levels are associated with an increased cardiovascular morbidity and mortality, with hypercholesterolemia being listed among the major cardiovascular risk factors (1).

A large number of prospective studies have consistently showed a direct and independent association between serum cholesterol and cardiovascular risk (2,3). This correlation appears to be linear, with no evidence of a threshold level above or below which there is a significant change in the slope of the regression line that describes the relationship between cholesterol and cardiovascular risk (1-3).

Low-density lipoprotein (LDL) cholesterol reduction, both in primary and secondary prevention trials, is associated with a significant cardiovascular risk reduction (4). There is also evidence showing that the magnitude of cardiovascular risk reduction associated with LDL cholesterol-lowering largely depends on pre-treatment LDL cholesterol levels, estimated cardiovascular risk and timing of the cholesterol-lowering intervention (5- 7). Clinical trials with statins and, more recently with ezetimibe, have reinforced the hypothesis that LDL cholesterol-lowering produces undeniable benefits in terms of cardiovascular risk prevention. In addition, it is largely accepted that the greatest cardiovascular risk reduction is obtained in patients reaching lower plasma LDL cholesterol levels (8,9).

The intensity of cholesterol-lowering should be proportional to the initial absolute plasma cholesterol levels, and to the patients' cardiovascular risk, the latter being estimable with specific algorithms and risk charts (1). Furthermore, the higher the patients' risk, more ambitious should be the therapeutic goal to be achieved for LDL cholesterol (1). Likewise, timeliness of cholesterol-lowering intervention is also crucial. This point arises from some considerations: 1) cardiovascular risk associated with cholesterol is cumulative, depending on time of exposure to circulating cholesterol levels (10); 2) patients with genetic forms of hypocholesterolemia (e.g., loss of function mutations of PCSK9 gene), that are characterized by low LDL cholesterol levels from birth, obtain greater cardiovascular risk reduction than it would be expected from their absolute plasma cholesterol levels (11); 3) early prescription of cholesterol-lowering therapy is

associated with better therapeutic compliance (12) and more effective prevention of cardiovascular events particularly in patients at higher risk (7, 13).

Treatment strategies to achieve optimal plasma LDL cholesterol levels include both lifestyle and pharmacological interventions. The initial therapeutic approach to hypercholesterolemia should always include non-pharmacological measures (1). Low dietary intake of cholesterol, saturated and "trans" fats and increased intake of dietary fiber, as well as exercise programs suited to the patients physical possibilities, are associated with LDL cholesterol reduction and exert beneficial effects on additional cardiovascular risk factors. Lifestyle changes are necessary as a first therapeutic approach in low risk subjects, but also in addition to drug therapy in patients at higher cardiovascular risk. Despite this evidence, the efficacy of lifestyle interventions is often hampered by some limitations: patients compliance is unsatisfactory and poor adherence and maintenance in the medium- to long-term is common (14). In addition, some dietary components with potential cholesterol-lowering activity are present in small amounts in food. Therefore, the use of nutraceuticals has become widespread in recent years. Nutraceuticals are nutrients and/or bioactive compounds of plant or microbial origin, with possible beneficial effects on human health when supplemented in adequate amounts (often above those present in foods). Nutraceuticals may be added to different foods and beverages (fortified foods, supplements), or taken in the form of dietary supplements (liquid preparations, tablets, capsules).

A growing number of nutraceuticals with variable cholesterol-lowering activity have been proposed and scientific research regarding some of them has produced conflicting results; in addition, reliability of a number of trials has been flawed by methodological limitations. Based on this background, the cholesterol-lowering activity of the most popular nutraceuticals (i.e., fiber, phytosterols, soy products, policosanol, red yeast rice and berberine) will be discussed along with: 1) the level of evidence on the cholesterol-lowering efficacy rising from interventional studies in humans; 2) the possible side effects associated with their use; 3) the categories of patients who could benefit from nutraceutical supplementation.

Fiber

Dietary fiber consists of the edible part of plants that is not digested in the human small intestine and pass through the large intestine quite intact. It includes non-starch polysaccharides (cellulose, hemicellulose, gums, pectins), oligosaccharides (inulin, fructo-oligosaccharides) and lignin.

From a functional point of view, dietary fiber is grouped into 4 classes (15):

1. insoluble, non-fermentable fiber (bran). It is an insoluble fiber that is poorly fermented in the intestine; it can exert mechanical laxative effects;
2. soluble, non-viscous, fermentable fiber (inulin, dextrin, oligosaccharides). It is quickly and easily fermented in the intestine. It does not cause increased viscosity and it is rapidly and completely fermented by the intestinal microbiota. It may have a prebiotic effect, but it does not exert laxative effects;
3. soluble, viscous, fermentable fiber (β-glucan, guar gum, pectin, glucomannan). It is quickly fermented and forms a viscous gel in water, increasing chime viscosity and reducing nutrients' absorption. It is rapidly fermented in the intestine, thus losing its laxative effects;
4. soluble, viscous, non-fermentable fiber (*psyllium*, methylcellulose). It reduces the absorption of nutrients due to its viscosity and exerts laxative effects.

The cholesterol-lowering effect of fiber is mainly due to its viscosity. Water soluble viscous fiber forms a gel that binds bile acids in the small intestine and increases their excretion in feces. Cholesterol is a major component of bile; hence, the increased bile acid fecal excretion leads to an increased liver use of cholesterol for bile production. The higher fiber viscosity, the greater its cholesterol-lowering potential (16,17).

It has been suggested that products of fiber fermentation in the gut (e.g., short-chain fatty acids) may exert favorable effects on lipid metabolism (18). Observational studies have shown that regular consumption of dietary fiber is associated with a significant cardiovascular risk reduction (19,20). In particular, for each increase of 10 g/day fiber consumption, especially from whole cereals and fruit, 14% reduction in the risk of

coronary events and 27% reduction of death from coronary heart disease has been observed (21). The lipid-lowering activity of fiber has been claimed to explain part of these beneficial effects. Several studies have explored the influence of fiber supplementation on plasma lipid levels. Fiber enriched diet, including higher amount of legumes, fruit and vegetables, reduces both total and LDL cholesterol levels (22-24). Conversely, the effect of whole grains on plasma lipid levels is still limited and controversial.

A consumption of approximately 35 g/day of fiber has been recommended for cardiovascular disease prevention. Nevertheless, the intake of fiber is far below the recommended daily dose worldwide (25-27); it happens also among Mediterranean populations, which traditionally consumed a larger amount of fiber (26,27). Therefore, in recent years, increasing interest has been addressed to the study of the cholesterol-lowering effect of different types of fiber added to the usual diet. Evidence from randomized controlled trials (RCTs) and meta-analyses is shown in Table 1. Overall, dietary supplementation with fiber including β-glucan (28,29), *psyllium* (28,30,31), pectin (28), guar gum (28) chitosan (32), glucomannan (33) and hydroxypropylmethylcellulose (34,35) reduced significantly plasma LDL cholesterol concentrations in healthy subjects, in patients with either hypercholesterolemia or with diabetes. Reductions of plasma LDL cholesterol levels have been observed also in trials evaluating the effect of fiber supplementation on top of statin therapy; some of these studies have been conducted for a fairly long period (up to six months).

The cholesterol-lowering effect of fiber ranges from 4% (chitosan) to 14% (guar gum), with possible variations in relation to the doses used in the different trials. It should be emphasized that this effect can be greater when the daily fiber intake is higher and that even higher doses are unlikely to cause significant side effects. The effect of fiber on triglycerides and high-density lipoprotein (HDL) cholesterol is less clear (Table 1), although some studies suggest a possible influence of fiber in reducing postprandial triglyceridemia (36,37). Additional RCTs are needed to provide a clear answer on whether dietary fiber is able to influence these lipid parameters. In addition to the lipid-lowering effects, fiber improves other parameters, such as plasma glucose and insulin levels, blood pressure and body weight (18).

In general, the quality of intervention studies conducted with added fiber are satisfactory and their results seem to be quite comparable. In fact, on the basis of current knowledge, fiber has been the object of a specific claim by the US Food and Drug Administration (FDA) (β-glucan and *psyllium*) and by the European Food Safety Authority (EFSA) (β-glucan, chitosan, glucomannan, guar gum, hydroxypropylmethylcellulose and pectin) for the maintenance of optimal cholesterol levels (Table 2).

In conclusion, a regular intake of fiber, mostly that with higher viscosity, reduces LDL cholesterol concentrations. When an adequate intake of fiber with diet alone is not feasible, the use of fiber-containing supplements can be an effective strategy to safely reduce cholesterol levels and possibly cardiovascular risk. Side effects related to excessive intake of fiber are unusual (38,39), except for symptoms of intestinal discomfort with higher doses (bloating, flatulence, meteorism) (39).

Overall, the use of added fiber may be advised when people are unable to increase their intake of dietary fiber with natural foods: 1) in the general population; 2) in patients with mild hypercholesterolemia and low to moderate cardiovascular risk; 3) in patients with mild hypercholesterolemia and/or metabolic syndrome. (Table 3)

Phytosterols

Phytosterols and their esterified derivatives, stanols, are bioactive compounds of plant origin; they are structurally similar to cholesterol and are poorly absorbed in the gut (0.5-2% for sterols and 0.04-0.2% for stanols). They are found in small amounts in fruits, vegetables, nuts, seeds, cereals, legumes and vegetal oils and their average dietary consumption is about 300 mg/day, although it may be higher in vegetarians (600 mg/day) (40).

The cholesterol-lowering effect of phytosterols is mainly due to their structural homology with cholesterol. Phytosterols reduce intestinal cholesterol absorption by competing with dietary and bile cholesterol. In the enterocytes, they are carried back into the intestinal lumen by the ATP-binding cassette sub-family G member 5 (ABCG5) and ABCG8 transporters and excreted in the faeces (41).

Cross-sectional studies have shown an inverse association between natural plant sterols intake and LDL cholesterol levels (42-44). In agreement with these findings, RCTs and meta-analyses show that an increased intake of phytosterols reduces significantly plasma total and LDL cholesterol levels by about 12 mg/dL (~8-10%) in healthy subjects and in patients with hypercholesterolemia (45-51) (Table 4). A similar cholesterol reduction has been observed in a meta-analysis of studies performed in diabetic patients (52) (Table 4). The effect of phytosterols on plasma triglycerides and HDL cholesterol levels is unclear. Clinical trials provide conflicting results and meta-analyses show no significant effect of supplementation of phytosterols on these parameters (47,51-53) (Table 4).

The cholesterol-lowering effect of phytosterols appears to be higher in patients with plasma LDL cholesterol levels above 160 mg/dL (45-48). Also, phytosterol-induced cholesterol-lowering is greater in patients with heterozygous than in patients with homozygous hypercholesterolemia (54). No evidence of interaction of phytosterols with most lipid-lowering drugs (statins, ezetimibe, fibrates) has been described. Moreover, an additive cholesterol-lowering effect has been described when phytosterols are taken in combination with statins and ezetimibe (40).

The efficacy of phytosterols in reducing plasma cholesterol levels is dose dependent for doses below 3 g/day; above this dose a plateau effect is commonly observed without any further significant LDL cholesterol-lowering effect. Moreover, it has been shown that the efficacy of phytosterols and stanols is similar up to a daily consumption of 2 g (55), the latter being the dose of phytosterols recommended by most scientific societies (1,56-58).

A sufficient intake of phytosterols is rarely provided by diet, even in vegetarians; therefore, phytosterols are used to enrich foods and drinks (e.g., margarine, yogurt drinks, cream cheese, bakery products) or may be part of specific supplements.

Phytosterols have no significant side effects when they are used at the recommended doses. However, an excessive intake of phytosterols may be associated with a reduced intestinal absorption of fat-soluble vitamins; therefore, patients taking high doses of phytosterols should be informed of this possible risk.

Sitosterolaemia is a rare autosomal recessive disease characterized by phytosterols' accumulation due to ABCG5 or ABCG8 gene mutations. Homozygosity for this condition is characterized by an abnormally high intestinal absorption of sterols, severe hypercholesterolemia, early atherosclerosis development and increased cardiovascular morbidity and mortality (59). Conversely, heterozygous patients are asymptomatic and can tolerate the intake of sterols with diet, although it has not still defined the threshold above which consumption of phytosterols may be harmful for these individuals. No side effects for regular consumption of 2 g/day of phytosterols have been recorded.

Data on the hypocholesterolemic effect of phytosterols derive from good quality intervention studies performed in a quite large number of subjects; overall, the results reported appear to be quite consistent. In this light, FDA and EFSA released a claim related to the use of phytosterols for LDL cholesterol reduction (Table 2). EFSA recommended not to exceed a dose of 3 g/day and suggests that patients receiving lipid-lowering medications should use phytosterols under medical supervision. FDA released a health claim recognizing the reduction of coronary artery disease risk for a dose of phytosterols up to 3.4 g/day. Similarly to most nutraceuticals, the cost of phytosterol supplementation should be considered, because continuous treatment is needed over time to maintain its cholesterol-lowering efficacy (Table 3).

In accordance with the major international scientific societies (1,56-58), the regular use of 2 g/day of phytosterols under medical supervision may be advised for reducing LDL cholesterol by 10%:

1) in patients with mild hypercholesterolemia and low to moderate cardiovascular risk, when drug therapy is not yet indicated; 2) in patients already on drug therapy who cannot achieve the recommended LDL cholesterol target levels;3) in patients with documented intolerance to multiple statins (Table 3).

Soy

Soy (Glycine max) is an East Asian native leguminous plant, rich in proteins (36-46%, depending on the variety), lipids (18%), soluble carbohydrates (15%) and fiber (15%). The high content of essential amino acids is a particular feature of soy compared to other legumes. Soy contains also several micronutrients such

as lecithin (0.5%), sterols (0.3%), isoflavones (0.1%), tocopherols (0.02%) and low levels of tocotrienols, lignans and sphingolipids (60). Nutritional properties and health benefits of soy have been studied for many years, with epidemiological observations suggesting an inverse relationship between soy consumption and cardiovascular risk. The cholesterol-lowering effect of soy is generally attributed to its isoflavone content. Isoflavones are phytoestrogens which are able to bind the estrogen receptor and to exert estrogen-like activity. They affect lipid metabolism either directly by modulating lipogenesis and lipolysis, or indirectly by regulating appetite and energy balance (61). Soybean processing thecniques, varieties of soy and culturing conditions influence the amount of soy isoflavones (62). Whole soybean, that is less consumed in Western countries, has the highest concentration of isoflavones, whose content decreases progressively with the increasing degree of soybean processing (62).

The cholesterol-lowering effect of soy (63) may be related also to its content in lecithin, phytosterols and β-glucan, which are able to reduce intestinal cholesterol absorption (60,64). Moreover, soy proteins including β-conglycinin (7S globulin) and glycinin (11S globulin), and peptides obtained by their intestinal hydrolysis may exert cholesterol-lowering effects by promoting LDL-receptor (LDLR) expression (65,66).

A meta-analysis of 38 studies performed between 1967 and 1994, concluded that soy proteins are able to reduce LDL cholesterol levels by 12.9% (67). This observation has prompted FDA to release a claim in 1999 (Table 2) stating that dietary intake of 25 g/day of soy protein can reduce cardiovascular risk (68). Several meta-analyses (50,69-76) have later demonstrated that soy protein-induced LDL cholesterol reduction ranged from 4% to 6% (Table 5). In 2012, EFSA has rejected a claim on the possible beneficial effects of soy because of lack of evidence of a clear cause-effect relationship (77). However, more recently Health Canada observed that 33% of interventional studies with either isolated or concentrated soy proteins found a significant reduction in plasma LDL cholesterol levels (78). Overall, trials performed in recent years have provided contradictory results on the cholesterol-lowering effects of soy (77-81).

The inconsistency of these data might have different explanations. Soy contains several bioactive components exerting a possible influence on plasma LDL cholesterol levels, although it is not clear which of

them is primarily responsible for the greatest cholesterol-lowering effect; type, dose and duration of soy supplementation and the different characteristics of the studied populations make results of these trials difficult to be interpreted and compared each other. Finally, it should be kept in mind that a statistically significant but modest reduction in plasma LDL cholesterol levels might not necessarily be associated with a significant clinical benefit, given the absence of data on cardiovascular outcomes. Therefore, since soy is a source of vegetable protein, fiber, unsaturated fats, vitamins, minerals and phytonutrients its dietary intake can be encouraged. In addition, consumption of soy products can be a useful substitute for animal source foods that naturally contain more saturated fat and cholesterol.

Evidence on the cholesterol-lowering effect of dietary supplementation with soy products is currently contradictory; thus, such supplementation may be advised but with some level of uncertainty: 1) in the general population; 2) in patients with mild hypercholesterolemia and low to moderate cardiovascular risk (Table 3).

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Policosanol

Policosanol (PCS) is a mixture of long chain linear aliphatic alcohols (octacosanol, tetracosanol, hexacosanol, and others) that are present in beeswax, potatoes, rice bran and in sugar cane (82). The mechanism behind PCS-induced cholesterol-lowering has not yet been fully elucidated. It has been suggsted that PCS inhibits 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMGCoA) reductase, thus reducing cholesterol synthesis (83,84). PCS has been used as lipid-lowering agent in Cuba since 1991; until 2004, scientific literature on the potential cholesterol-lowering effect of PCS was derived from studies in Cuba (85-99). These studies (100,101) showed that sugar cane-derived PCS reduced LDL cholesterol similarly to statins and more than plant sterols; in addition, PCS raised plasma HDL cholesterol levels without significant side effects (Table 6). PCS-induced cholesterol-lowering seems to be dose dependent in a dose range of 2 to 40 mg/day. More recently, the beneficial effects of PCS on plasma cholesterol levels have been questioned by the results of several RCTs performed in Europe and the US; these RCTs failed to find any

significant effect of PCS on plasma cholesterol levels in different clinical settings. The lack of cholesterol-lowering efficacy has been confirmed for both Cuban sugar cane-derived PCS (102,103) and for PCS extracted from different sources (104,105). In 2011, EFSA rejected a claim on the beneficial effects of PCS for lack of evidence of a cause-effect relationship between PCS supplementation and cholesterol-lowering (106).

Without consistent data on the cholesterol-lowering efficacy from different and independent research groups, the use of PCS cannot be advised for cholesterol-lowering.

Red yeast rice

Red yeast rice (RYR) is a fermented product of rice used for centuries in China for the preparation of rice wine, as a flavor enhancer, as a food coloring and for therapeutic purposes as "aid for digestion and circulation" (107). Fermentation of red rice by the yeast *Monascus purpureus* produces, among the others, monacolin K, a monacolin that is structurally and functionally similar to lovastatin (107,108). Monacolin K is able to inhibit HMGCoA reductase and cholesterol synthesis. The cholesterol-lowering efficacy of RYR might be only in part attributable to monacolin K. Accordingly, RYR contains at least 10 different monacolins, many of them with supposed HMGCoA reductase inhibitory activity. Furthermore, RYR contains phytosterols, which are able to reduce intestinal cholesterol absorption, as well as fiber and niacin, which exert cholesterol-lowering effects (108,109). Several trials have reported that RYR is effective and safe in the treatment of patients with mild to moderate hypercholesterolemia. Placebo-controlled trials, some of these lasting more than four years, have confirmed the cholesterol-lowering effect of RYR, with a reduction of total cholesterol ranging from 16% to 31% and of LDL cholesterol from 22% to 32% (110). The prescribed daily dose of RYR was variable in these trials, as well as the content of monacolin K of the different RYR preparations (Table 7); in some of these trials, the dose of monacolin K exceeded 10 mg/day.

The first prospective double-blind placebo-controlled trial in the American population has been performed in 1999 (111). Untreated patients with hyperlipidemia were randomized to receive either 2.4 g/day of RYR

or placebo for 12 weeks. At the end of the study, LDL cholesterol levels were significantly different between the two groups compared to baseline; LDL cholesterol levels decreased by 39 ± 19 mg/dL (22%) in the group receiving RYR and 5 ± 22 mg/dL (5%) in the placebo group. No adverse events were reported in the two treatment arms (111). Additional clinical trials with RYR and meta-analyses (112-115) have reported similar results in different study populations (Table 7). In a meta-analysis of thirteen randomized placebo-controlled trials (113) including over 800 dyslipidemic patients, RYR reduced significantly LDL cholesterol levels by 34 mg/dL compared to placebo; the cholesterol-lowering effect of RYR was neither related to the dose and the duration of the nutraceutical supplementation nor it was associated with significant side effects.

Similar results have been reported in other meta-analyses (112,114,115), confirming the cholesterol-lowering efficacy of RYR and its good safety profile. In particular, a meta-analysis by Gerard et al. (114) showed that the incidence of muscle, hepatic and renal adverse events was comparable between RYR and placebo; overall, the clinical relevance of the possible adverse events of RYR were moderate, but it must be underlined also the incomplete reporting of safety data in most individual trials included in this meta-analysis (114).

Randomized trials have investigated the safety profile of RYR in patients who discontinued or refused treatment with statins. RYR tolerability was compared with that of pravastatin in patients with a history of statin-induced myalgia (116). Comparable LDL cholesterol reductions (30% and 27% in the RYR group and in the pravastatin group, respectively) were achieved in both treatment groups, with also a low prevalence of myalgias (5% and 9% in the RYR group and in the pravastatin group, respectively). In patients with statin intolerance, supplementation with 3.6 g/day of RYR reduced plasma LDL cholesterol levels by 27% compared to placebo, with a comparable safety profile between RYR and placebo (117). Particularly, pain scale, serum creatine phosphokinase and liver enzyme levels did not differ in the two groups.

The impact of RYR on cardiovascular prognosis has been studied in the “China Coronary Secondary Prevention Study” (118); this trial recruited 4870 patients with previous myocardial infarction and moderate

hypercholesterolemia, randomized to receive either *Xuenzhikang* (i.e., a purified extract of RYR containing 5-6.4 mg of monacolin K) or placebo for 5 years. *Xuenzhikang* reduced plasma LDL cholesterol levels by 20% and the risk of coronary heart disease events by 45% compared to placebo. Moreover, treatment with *Xuenzhikang* also reduced significantly total mortality by 33%, cardiovascular mortality by 30% and coronary revascularizations by 33%, with a comparable safety profile to placebo. Improvement of endothelial function following RYR spplmentation (119) futher supports the possible cardiovascular protective effect of RYR. The "Task Force for the management of dyslipidemias of the European Society of Cardiology and the European Atherosclerosis Society" included RYR among those nutraceuticals with a documented cholesterol-lowering activity (1).

On the basis of the quality and consistency of the data present in the literature in 2011, EFSA endorsed the cause-effect relationship between use of RYR and maintenance of an adequate plasma LDL cholesterol concentration in the general adult population; this effect would be reached with a dose of 10 mg/day of monacolin K. Monacolin K is subjected to the same restrictions of lovastatin. In 2007, a claim by FDA underlined the potential risks arising from online shopping of products containing RYR. Since 2007, FDA did not release further advices on this topic (Table 2). In 2016, the Joint Commission of Experts of the Federal Office of Consumer Protection and Food Safety (BVL) and the Federal Institute for Drugs and Medical Devices (BfArM) in Germany has decided that products with a monacolin K dose of 5 mg per day have a significant pharmacological/metabolic action and therefore should be classified as drugs.

Safety of different preparations containing RYR is debated, in part because composition of products containing RYR is quite variable (120). For instance, commercial preparations labeled as containing 600 mg of RYR per capsule, have been reported to contain variable amounts of monacolin K, ranging from 0.31 to 11.15 mg/capsule. Moreover, some RYR preparations contained citrinin (121), a mycotoxin with possible renal toxicity. Therefore, the use of commercial preparations of RYR should be supported by adequate demonstration of purity, safety and cholesterol-lowering efficacy.

On the basis of current knowledge, the use of RYR preparations containing a monacolin K dose ≤10 mg/day can be advised in patients with mild to moderate cardiovascular risk and LDL cholesterol levels exceeding th recommended therapeutic targets by 20-25% or less, despite adequate lifestyle changes have been implemented (Table 3).

Berberine

Berberine (BBR) is an isoquinoline alkaloid that is extracted from different plants, including Berberis vulgaris, Coptis chinensis, Berberis aristata (122). BBR has anti-microbial, immune-modulatory, anti-tumoral and metabolic effects (122). Additional favorable effects of BBR on cardiovascular system have been proposed, considering that BBR promotes vasodilation, reduces the risk of congestive heart failure, cardiac hypertrophy and arrhythmias (123). The cholesterol-lowering effect of BBR have been related to different mechanisms of action. BBR promotes an increased expression and half life of the LDLR on the hepatocyte surface (124); the transcriptional activity of the LDLR promoter is increased by BBR-induced stimulation of the activation of JNK/c-jun. Also, LDLR mRNA is stabilized by ERK modulation (125). Overall, all these effects promote an increased expression of the LDLR. In addition, BBR reduces the expression of PCSK9 in vitro; because PCSK9 promotes lysosomal degradation of the LDLR, BBR-induced PCSK9 inhibition might increase LDLR availability (126). Finally, BBR-induced activation of AMPK, which in turn inactivates HMGCoA reductase (127), may have a role in cholesterol- and triglyceride-lowering.

A study evaluating the effect of BBR in patients with hypercholesterolemia has shown significant cholesterol- and triglyceride-lowering effects of BBR, with 25% and 35% reductions of plasma LDL cholesterol and triglyceride levels, respectively (125); these effects were more pronounced in patients not receiving other lipid-lowering drugs.

The lipid-lowering effects of BBR have been evaluated in three meta-analyses (128-130, Table 8). Dong et al. (128,129) performed two meta-analyses of trials in patients with hypercholesterolemia and/or type 2

diabetes. The dose of BBR used in the different trials ranged from 0.5 g to 1.5 g/day. These meta-analyses reported similar findings: BBR was associated with a 25 mg/dL decrease of plasma LDL cholesterol levels, along with a significant reduction of plasma triglyceride level and a mild but significant increase of plasma HDL cholesterol concentrations (Table 8).

The lipid-lowering efficacy of BBR was compared with that of simvastatin. In patients with hypercholesterolemia, a 2-month treatment with either BBR, simvastatin or their combination, reduced plasma total cholesterol, LDL cholesterol and triglyceride levels (131). Combination therapy reduced plasma LDL cholesterol levels compared to the individual active treatments. Moreover, adding BBR to simvastatin improved the mild statin-induced triglyceride-lowering of simvastatin alone (131). Possible side effects of BBR emerged mostly in those trials using the highest doses of BBR; side effects included constipation, diarrhea, abdominal distension and bitter taste in the mouth (129). Repeated oral administration of BBR reduced the CYP2D6, CYP2D9 and CYP3A4 cytochrome activity in healthy subjects (132); thus, possible interactions between BBR and drugs that use the same degradation pathways need to be considered. Although results from intervention studies with BBR are quite consistent, it should be noted that almost all interventional trials with BBR have been performed in Asian populations, that makes results' generalizability difficult. Moreover, bioavailability of the different BBR preparations is a matter of debate. Accordingly, the intestinal absorption of BBR is often minimal and with a wide inter-individual variability; this issue could be responsible for a possible variability in the lipid-lowering efficacy of the different BBR preparations.

Neither EFSA nor FDA have released yet specific claims on the cholesterol-lowering efficacy and safety of BBR.

Based on current knowledge, if the results observed in Asian populations would be confirmed in other ethnic groups, the use of BBR at a dose of 0.5-1.5 g/day could be advised in:

1) patients at mild to moderate cardiovascular risk with LDL cholesterol levels exceeding recommended therapeutic goals by 20% or less, despite lifestyle changes have been implemented; 2) patients with mild to

moderate hypercholesterolemia and metabolic syndrome, in particular those with modest increases in triglycerides or initial dysglycemia, possibly in combination with a statin; 3) patients with different levels of risk in which there is a clear and documented intolerance to multiple statins or who refuse statin treatment (Table 3).

Nutraceutical combinations

Evidence reporting the cholesterol-lowering efficacy of different nutraceuticals has raised considerable interest on this topic and prompted the development of novel preparations containing multiple nutraceuticals with the aim to reach greater total and LDL cholesterol reductions.

The possibility to combine different nutraceuticals arises from two main speculative assumptions: 1) to exploit the possible complementary lipid-lowering effects of each nutraceutical; 2) to reduce nutraceutical doses in order to ensure tolerability while maintaining the lipid-lowering efficacy. To date, few RCTs have been performed to support this assumptions.

The effect of combining fiber and phytosterols has been presented in a review of interventional studies, in normolipidemic and moderately hypercholesterolemic individuals (133); an average reduction of plasma total and LDL cholesterol levels of 8 and 11%, respectively, has been reported. The variety of fiber supplements combined with phytosterols strongly affects the cholesterol-lowering efficacy. In addition, two studies comparing the effect of the individual components versus their combination, revealed a slightly higher cholesterol-lowering effect of the nutraceutical combination (134,135).

The combination of phytosterols and RYR did not provide an additional cholesterol-lowering effect compared to the individual nutraceuticals (136).

The combination of RYR, BBR, PCS, astaxanthin (ASX), coenzyme Q10 (CoQ10) and folic acid (FA) reduced plasma LDL cholesterol levels by 25%, without relevant side effects (137). This combination reduced total cholesterol, LDL cholesterol and triglycerides in patients with hypercholesterolemia (138); moreover, the same nutraceutical combination reduced HOMA index, suggesting a possible positive effect

on insulin sensitivity. Additional studies have been performed using the combination of RYR/BBR/PCS/ASX/CoQ10/FA; specifically, patients with polygenic hypercholesterolemia, coronary artery disease, statin intolerance, and children with either heterozygous familial hypercholesterolemia or familial combined hyperlipidemia have been treated with this nutraceutical combination (139-145). Overall, these studies confirmed the LDL cholesterol-lowering efficacy of the nutraceutical combination (from -15% to 32%), with a greater cholesterol reduction in patients with higher pre-treatment LDL cholesterol levels. A recent systematic review and meta-analysis of RCTs showed that the combination of RYR/BBR/PCS/ASX/CoQ10/FA was associated with significant reductions of plasma total cholesterol (−26.15 mg/dL), LDL cholesterol (−23.85 mg/dL), triglyceride (−13.83 mg/dL) and glucose levels (−2.59 mg/dL), and a modest but significant increase of plasma HDL cholesterol levels (2.53 mg/dL) (146). Finally, small sample size studies have shown that the same nutraceutical combination was able to improve endothelial function, aortic stiffness, endothelial injury and low-grade systemic inflammation (138,139,147). Although the use of nutraceutical combinations might have possible advantages in terms of efficacy and tolerability, evidence is still lacking on the potential additive/synergistic cholesterol-lowering effects of the different nutraceuticals. Finally, the cholesterol-lowering benefit provided by the addition of PCS to any nutraceutical combination is questionable.

Common issues of nutraceutical supplementation

Although health benefits may arise from the use of different nutraceuticals with cholesterol-lowering activity, their use might be also associated with possible risks, some of which are common to all nutraceuticals whereas other risks are related to specific nutraceuticals.

Single-center design, short duration of supplementation and small sample size of most trials testing the cholesterol-lowering efficacy of nutraceuticals are the main limitations. Hence, despite a number of meta-analyses have been published confirming the beneficial influence of some nutraceuticals on lipid profile, results of larger multicenter trials are desirable.

The independent buying and use of nutraceuticals might encourage patients under pharmacological treatment to reduce or discontinue medications without a prior consult with physicians. In agreement with this possibility, propensity to self-treatment and poor compliance to drug therapy has been recorded among statin-treated patients who were informed on the possible beneficial effects of phytosterols (148-149). Overall, the use of cholesterol-lowering nutraceuticals should not be considered as the “safe alternative” to pharmacological intervention. This is particularly true in patients with genetic forms of hypercholesterolemia and in other categories of patients at high or very high cardiovascular risk.

Another point to consider is that the cost of all fortified foods is far higher than that of non-fortified foods. In 2008, EFSA reported that the cost/kg of plant sterols-enriched products can be up to 4-times higher than that of non-enriched products (150). Similarly, the cost of products containing RYR and BBR is higher than that of generic statins. Hence, if we consider the significant relationship between socioeconomic status and dietary habits (151,152), the cost of most nutraceuticals can potentially interfere with their regular purchasing and, consequently, with adherence and persistence to supplementation. This is a crucial point, because as for cholesterol-lowering drugs, the therapeutic effect of nutraceuticals is expected to be closely related to their regular use. Finally, the large and uncontrolled availability of nutraceutical preparations (e.g., supermarkets, e-commerce, drugstores) and the possibility that their use may be suggested by physicians, nutritionists, dietitians, but also friends, relatives, or decided upon by the patients themselves might predispose to the risk of incorrect consumption of these preparations and to the consequent side effects. This risk might be higher for those nutraceuticals with "pharmacological" properties.

This statement highlights the need for a close collaboration between physicians, nutritionists, health care professionals and patients in order to prevent the widespread improper and uncontrolled use of nutraceuticals. In order to promote a safe and rational use of specific nutraceuticals, competent authorities and caregivers should ensure careful monitoring of prescriptions, self-medications, the adequacy of doses and compliance to nutraceutical supplementation. A key role in many of these processes should be played by physicians, that should be aware of the possible risks of an incorrect use of cholesterol-lowering

nutraceuticals; however, they should also consider the potential benefit of a controlled use of single nutraceuticals or rational combinations of nutraceuticals.

Conclusions

Based on current literature, the cholesterol-lowering effect of some nutraceuticals (fiber, phytosterols, RYR) is consistent and supported by a good level of scientific evidence (Table 9). Therefore, their use may be advised in some particular categories of patients, as reported in Table 3. With regard to BBR, there is sufficient evidence showing significant cholesterol-lowering effects, although these effects emerged from interventional studies carried out almost exclusively in Asian populations, thus making these results difficult to be generalized to other ethnic groups (Table 9). Data on the cholesterol-lowering effects of soy are conflicting and, therefore, the strength of the recommendation is quite low, whereas the scientific evidence is inconclusive for PCS (Table 9). Among the different nutraceuticals combinations, there is evidence supporting the cholesterol-lowering efficacy and safety of low doses of RYR/BBR/PCS/ASX(CoQ10/FA; however, on the basis of the available data, there is still no demonstration of an additive/synergistic cholesterol-lowering effect of the single nutraceuticals used in this combination.

Therefore, the most relevant conclusions of this statement may be synthesized as follows:

1) On the basis of data present in the literature some nutraceuticals (added fiber, phytosterols, red yeast rice) may help control hypercholesterolemia;

2) Of course, the above nutraceuticals may be of help only in subjects who do not yet need pharmaceutical treatments, or in addition to drug therapy.

Table 1. Meta-analyses and randomized controlled trials in humans on the lipid-lowering effects of different types of fiber

Fiber	Type of study	Subjects (Number, Type)	Average dose (range)	Mean duration (range)	Observed effects	Ref.
β-glucan (oats)	Meta-analysis of 25 RCT	n:1600 Healthy subjects Hypercholesterolemia Diabetes mellitus	5.0 g/day (2-30 g/day)	6 weeks (2-12 weeks)	↓ LDL-C: -6.2 mg/dl No effect on TG and HDL-C	(28)
	Meta-analysis of 28 RCT	n:2529 Healthy subjects Hypercholesterolemia Type 2 Diabetes	(3-12.4 g/day)	2-12 weeks	↓ LDL-C: -9.6 mg/dl No effect on TG and HDL-C	(29)
Psillyum	Meta-analysis of 17 RCT	n:757 Healthy subjects Hypercholesterolemia	9.1 g/day (2-30 g/day)	7 weeks (2-56 weeks)	↓ LDL-C: -10 mg/dl No effect onTG and HDL-C	(28)
	Meta-analysis of 21 RCT	n: 1717 Hypercholesterolemia	(3-20 g/day)	(2-26 weeks)	↓ LDL-C: - 11 mg/dl No effect on TG	(30)
	RCT	n:187 Hypercholesterolemia on pharmacological treatment	14 g/day	8 weeks	↓ LDL-C: -11 mg/dl (-6%) ↓ TG: -20 mg/dl (-17%) No effect on HDL-C	(31)
Pectin	Meta-analysis of 7 RCT	n: 277 Healthy subjects Hypercholesterolemia Diabetes mellitus	4.7 g/day (2-30 g/day)	5 weeks (4-6 weeks)	↓ LDL-C: -9.9 mg/dl No effect on TG and HDL-C	(28)
Guar gum	Meta-analysis of 18 RCT	n: 356 Healthy subjects Hypercholesterolemia Diabetes mellitus	17.5 g/day (2-30 g/day)	66 days (4-24 weeks)	↓ LDL-C: -22 mg/dl No effect on TG and HDL-C	(28)
Chitosan	Meta-analysis of 9 RCT	n:1219 Healthy subjects	3.7 g/day (0.24-15 g/day)	8.3 weeks (4-24 weeks)	↓ LDL-C: -6.2 mg/dl ↑ HDL-C: 1.2 mg/dl ↓ TG: -11 mg/dl	(32)
Glucomannan	Meta-analysis of 14 RCT	n: 531 Healthy subjects Hypercholesterolemia Diabetes mellitus	(1.2-15.1 g/day)	(3-16 weeks)	↓ LDL-C: -16 mg/dl ↓ TG: -11 mg/dl No effect on HDL-C	(33)
HPMC	RCT	n:52 Hypercholesterolemia	A: 5 g/day B: 15 g/day	8 weeks	A: ↓ LDL-C: -14 mg/dl No effect on TG and HDL-C B: ↓ LDL-C: -14 mg/dl No effect on TG and HDL-C	(34)
	RCT	n:13 Hypercholesterolemia on pharmacological treatment	5 g/day	4 weeks	↓ LDL-C: (-10%) No effect on TG and HDL-C	(35)

↑: increase, ↓: reduction, HDL-C: HDL-cholesterol, LDL-C: LDL-cholesterol, HPMC: hydroxypropyl-methylcellulose , TG: triglycerides, RCT: randomized controlled trials.

Table 2. Claims released by EFSA and FDA on nutraceuticals with cholesterol-lowering activity

Nutraceutical	Effective dose evaluated in the *claim*	EFSA	FDA
Fiber:			
β-glucan*	≥ 3 g/day	Reduction of LDL-C	Reduction del LDL-C Reduction of CHD risk
Chitosan	3 g/day	Maintenance of normal levels of LDL-C	-
Glucomannan	4 g/day	Maintenance of normal levels of LDL-C	-
Guar gum	10 g/day	Maintenance of normal levels of LDL-C	-
HPMC	5 g/day	Maintenance of normal levels of LDL-C	-
Pectin	6 g/day	Maintenance of normal levels of LDL-C	-
Psyllium	≥ 7 g/day	-	Reduction of LDL-C
Phytosterols	3 g/day	Reduction of LDL-C	Reduction of LDL-C
Soy derivatives	25 g/day	-	Reduction of CV risk
Policosanol	-	-	-
Red Yeast Rice	10 mg/day of monacolin K	Maintenance of normal levels of LDL-C	Monacolin K has the same restrictions to which is subjected lovastatin.
Berberine	-	-	-

* From oats and barley, CHD: coronary heart disease, LDL-C: LDL cholesterol, CV: cardiovascular, HPMC: hydroxypropylmethylcellulose.

Table 3. Advantages, disadvantages and possible indications of cholesterol-lowering nutraceuticals

	Advantage	Disvantages	Possible indication
Fiber	- LDL-C reduction by 4-14% - Effect on other CV risk factors - Relatively low-cost	Intestinal discomfort for excessive doses	- General population that fails to increase fiber intake with diet alone - Patients with mild hypercholesterolemia and low to moderate cardiovascular risk * - Patients with mild hypercholesterolemia and metabolic syndrome
Phytosterols	- LDL-C reduction by 8-10% - No interaction with lipid-lowering drugs	- Self purchasing by patients and risk of no medical supervision - Possible excessive intake with the risk of reduced absorption of fat soluble vitamins - High cost	- Patients with mild hypercholesterolemia and low to moderate cardiovascular risk * - Patients with intolerance to multiple statins - In addition to drug therapy for patients who do not reach optimal levels of LDL-C
Soy products	- LDL-C reduction by 4-13%	- Self purchasing by the patient - Risk of allergies - High cost	- General population - Patients with mild hypercholesterolemia and low to moderate cardiovascular risk *
Red Yeast Rice	- LDL-C reduction by 16-25% - Good safety profile - Reduction of cardiovascular risk	- Variability of composition and purity of OTC products - Self purchasing by patients and risk of no medical supervision - Higher cost compared to generic statins - Possible side effects at high doses	- Patients with mild to moderate hypercholesterolemia and low to moderate cardiovascular risk **
Berberine[§]	- LDL-C reduction by 20% - Better safety profile in patients with intolerance to multiple statins - Favorable effect on TG, HDL-C and blood glucose	- Variability of intestinal absorption - Self purchasing by patients and risk of no medical supervision - Higher cost compared to generic statins	- Patients with mild to moderate hypercholesterolemia and low to moderate CV risk *** - Patients with mild hypercholesterolemia and metabolic syndrome[†] - Patients with intolerance to multiple statins - In addition to drug therapy for patients who do not reach optimal levels of LDL-C

* patients requiring a reduction of LDL cholesterol by up to 10-15%, ** patients requiring a reduction of LDL cholesterol by up to 20-25%, *** patients requiring a reduction of LDL cholesterol by up to 20%, [§] studies performed almost exclusively in Asian populations and therefore not easily transferable to other populations, [†] Even in combination with a statin, in patients with modest increase in serum triglycerides and/or blood glucose. HDL-C: HDL cholesterol, LDL-C: LDL cholesterol, CV: cardiovascular; TG: triglycerides; OTC: over the counter.

Table 4. Meta-analyses of randomized controlled trials in humans on the lipid-lowering effects of phytosterols

Type of study	Subjects (Number, Type)	Average dose (range)	Mean duration (range)	Observed effect	Ref.
Meta-analysis of 49 RCT	n: >4500 Healthy subjects Hypercholesterolemia	(0.3-9 g/day)	(3-26 weeks)	↓ LDL-C: - 12 mg/dl	(46)
Meta-analysis of 20 RCT	n: 1273 Healthy subjects Hypercholesterolemia	2.08 g/day (0.45-3.2 g/day)	(2-52 weeks)	↓ LDL-C: -14 mg/dl (-6/-15%) No effect on TG and HDL-C	(47)
Meta-analysis of 84 RCT	n: 6805 Healthy subjects Hypercholesterolemia	2.15 g/day (0.45–9 g/day)	(21-182 days)	↓ LDL-C: -13 mg/dl (-8.8%)	(48)
Meta-analysis of 41 RCT	n: 2084 Healthy subjects Hypercholesterolemia	1.6 g/day (0.3-3.2 g/day)	28 days (21-315 days)	↓ LDL-C: -13 mg/dl (-8.5%) No effect on HDL-C	(49)
Meta-analysis of 124 RCT	Healthy subjects Hypercholesterolemia	2.1 g/day (0.2–9 g/day)	At least 2 weeks	↓ LDL-C: -6/12%.	(50)
Meta-analysis of 6 RCT*	n: 453 Familial Hypercholesterolemia	(1.6-2 g/day)	(4-8 weeks)	↓ LDL-C: -25 mg/dl No effect on TG and HDL-C	(51)
Meta-analysis of 5 RCT	n: 148 Diabetes mellitus	(1.8-3 g/day)	(3-12 weeks)	↓ LDL-C: -12 mg/dl No effect on TG and HDL-C	(52)
Meta-analysis of 12 RCT	n: 935 Hypercholesterolemia	(0.8-4 g/day)	(3-4 weeks)	↓ TG: -11 mg/dl (-6%) No effect on HDL-C	(53)

*2 studies with supplementation of stanols and 5 studies with supplementation of sterols, ↑: increase, ↓: reduction, HDL-C: HDL cholesterol, LDL-C: LDL cholesterol, TG: triglycerides, RCT: randomized controlled trials.

Table 5. Meta-analyses of randomized controlled trials in humans on the lipid-lowering effects of soy

Type of study	Subjects (Number, Type)	Average dose (range)	Mean duration (range)	Observed effect	Ref.
Meta-analysis of 38 RCT	n: 743 Healthy subjects Hypercholesterolemia	Soy proteins 47 g/day (18-124 g/day)	-	↓ LDL-C: -12.9% ↓ TG: -10.5% ↑ HDL-C: 2.4%	(67)
Meta-analysis of 10 RCT	n: 959 Healthy subjects Hypercholesterolemia	Soy proteins (19-60 g/day) Isoflavones (1-95 mg/day)	At least 14 days	↓ LDL-C: -6.56 mg/dl ↑ HDL-C: 1.16 mg/dl	(69)
Meta-analysis of 8 RCT	n: 639 Healthy subjects Hypercholesterolemia	Soy proteins (25-100 g/day) Isoflavones (3-132 mg/day)	-	↓ LDL-C: -5.79 mg/dl	(70)
Meta-analysis of 23 RCT	n:1833 Healthy subjects Hypercholesterolemia	Isoflavones (3-185 mg/day)	(4-26 weeks)	↓ LDL-C: -5.25% ↓ TG: -7.27% ↑ HDL-C: 3.03%	(71)
Meta-analysis of 43 RCT	n: 1756 Healthy subjects Hypercholesterolemia	Soy proteins (20-106.2 g/day) Isoflavones (2-192.4 mg/day)	(3-52 weeks)	↓LDL-C -4.25 mg/dl ↓ TG: -6.26 mg/dl ↑ HDL-C: 0.77 mg/dl	(72)
Meta-analysis of 11 RCT	n: 430 Healthy subjects Hypercholesterolemia	Soy proteins (25-133 g/day) Isoflavones (0-317.9 mg/day)	(3-14 weeks)	↓ LDL-C: -4.98% ↓ TG: -0.69% ↑ HDL-C: 3.00%	(73)
Meta-analysis of 30 RCT	n: 2913 Healthy Hypercholesterolemia	Soy proteins 26.9 g/day (15-40 g/day)	(4-52 weeks)	↓ LDL-C: -8.88 mg/dl (~6%) ↓ TG: -7.70 mg/dl ↑ HDL-C: 2.74 mg/dl	(74)
Meta-analysis of 43 RCT	Healthy subjects Hypercholesterolemia	Soy proteins <65 g/day	(4-18 weeks)	↓ LDL-C: from - 4.2 to -5.5% ↓ TG: -10.7% ↑ HDL-C: 3.2%	(75)
Meta-analysis of 8 RCT	n: 183 Type 2 Diabetes mellitus	Soy proteins (30-111 g/day) Isoflavones (0-132 mg/day)	(6-208 weeks)	↓ LDL-C: -11.6 mg/dl ↓ TG: -19.5 mg/dl ↑ HDL-C: 1.9 mg/dl	(76)
Meta-analysis of 14 RCT	Familial Hypercholesterolemia	-	-	↓ LDL-C: 4.6 mg/dl ↓ TG: -22 mg/dl ↑ HDL-C: 2.7 mg/dl	(51)

↑: increase, ↓: reduction, HDL-C: HDL cholesterol, LDL-C: LDL cholesterol, TG: triglycerides, RCT: randomized controlled trials.

Table 6. Meta-analyses and randomized controlled trials in humans on the lipid-lowering effects of policosanol

Type of study	Subjects (Number, Type)	Average dose (range)	Mean duration (range)	Observed effect	Ref.
Meta-analysis of 30 RCT	Healthy subjects Hypertension Hypercholesterolemia Type 2 Diabetes	12 mg (5–40 mg)	29.6 weeks (4–104 weeks)	↓ LDL-C: - 23.7% ↓ TG: -12.45%; ↑ HDL-C: 10.6%	(101)
RCT	Hypercholesterolemia Familial Hypercholesterolemia	20 mg	12 weeks	HyperC: ↓ LDL-C: -6% ↓ HDL-C: -5.5% ↑ TG: 9.6% FH: ↑ LDL-C: 3% ↑ HDL-C: 2.5% ↓ TG: -9.8%	(102)
RCT	n: 143 Hypercholesterolemia Mixed hyperlipidemia	10 - 80 mg	12 weeks	↓ LDL-C: -2% to -9% ↓ TG: -10% to -20% ↑ HDL-C: 0.6% to 4.6%	(103)
RCT	n:40 Hypercholesterolemia	20 mg	8 weeks	↓ LDL-C: -7.7% ↓ TG: -1.3% ↓ HDL-C: -3.3%	(105)

↑: increase, ↓: reduction, HDL-C: HDL cholesterol, LDL-C: LDL cholesterol, TG: triglycerides, HyperC: Hypercholesterolemia, FH: Familial Hypercholesterolemia, RCT: randomized controlled trials.

Table 7. Meta-analyses of randomized controlled trials in humans on the lipid-lowering effects of red yeast rice

Type of study	Subjects (Number, Type)	Content of monacolin K	Mean duration (range)	Observed effect	Ref.
Meta-analysis of 93 RCT	n: 9625 Dyslipidemia	3-12.4 mg/day	8 weeks (4-24 weeks)	↓ LDL-C: -28 mg/dl ↓ TG: -36 mg/dl ↑ HDL-C: 5.8 mg/dl	(112)
Meta-analysis of 13 RCT	n: 804 Dyslipidemia	2-11.4 mg/day	12 weeks (4-24 weeks)	↓ LDL-C: -34 mg/dl ↓ TG: -20 mg/dl No effect on HDL-C	(113)
Meta-analysis of 20 RCT	n: 2811 Dyslipidemia, Type 2 Diabetes, CHD, Hypertensive	4.8-24 mg/day	23 weeks 4-168 weeks	↓ LDL-C: -39 mg/dl ↓ TG: -23 mg/dl ↑ HDL-C: 2.7 mg/dl	(114)
Meta-analysis of 21 RCT	n: 4558 Hypertensive	(RYR 1200-1800 mg/day)	4-234 weeks	↓ LDL-C: -24 mg/dl No effect on TG and HDL-C	(115)

↑: increase, ↓: reduction, HDL-C: HDL cholesterol, LDL-C: LDL cholesterol, CHD: coronary heart disease, RYR: red yeast rice, TG: triglycerides, RCT: randomized controlled trials.

Table 8. Meta-analyses of randomized controlled trials in humans on the lipid-lowering effects of berberine

Type of study	Subjects (Number, Type)	Average dose (range)	Mean duration (range)	Observed effect	Ref.
Meta-analysis of 14 RCT	n: 1068 Type 2 Diabetes	0.5-1.5 g/day	12 weeks (8-24 weeks)	↓ LDL-C: -13/-22 mg/dl ↓ TG: -19/-45 mg/dl ↑ HDL-C: 0.8/2.7 mg/dl	(128)
Meta-analysis of 11 RCT	n: 874 Dyslipidemia, Type 2 Diabetes	0.5-1.5 g/day	15 weeks (8-52 weeks)	↓ LDL-C: -25 mg/dl ↓ TG: -44 mg/dl ↑ HDL-C: 1.9 mg/dl	(129)
Meta-analysis of 6 RCT	n: 451 Dyslipidemia	0.6-1.5 g/day	11 weeks (8-17 weeks)	↓ LDL-C: -25 mg/dl ↓ TG: -35 mg/dl ↑ HDL-C: 2.7 mg/dl	(130)

↑: increase, ↓: reduction, HDL-C: HDL cholesterol, LDL-C: LDL cholesterol, TG: triglycerides, RCT: randomized controlled trials.

591 **Table 9.** LDL-C reduction, levels of evidence and strength of recommendation
592 for different cholesterol-lowering nutraceuticals.

	Degree of LDL cholesterol reduction	Level of evidence	Strength of recommendation
Fiber	+	I	A
Phytosterols	+	I	A
Soy derivatives	+/-	II	C
Policosanol	-	VI	D
Red Yeast Rice	++	I	A
Berberin	++	*	*

Levels of evidence and strength of recommendation according to the Italian standard of care for diabetes (153):
Levels of evidence:
I: evidence obtained from multiple randomized controlled trials and/or from systematic reviews of randomized controlled trials;
II: evidence obtained from one randomized trial;
VI: *consensus* of experts.
Strength of recommendation:
A: strongly recommended;
C: basic uncertainty;
D: no recommendation.
* The level of evidence would be I, because supported by meta-analysis of interventional studies, and strength of recommendation A; however, because these studies were conducted almost exclusively in Asian populations, the data are not easily transferable to other ethnic groups.

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***Highlights (for review)**

- The cholesterol-lowering activity of some nutraceuticals (i.e. fiber, phytosterols, soy products, policosanol, red yeast rice and berberine) has been reviewed.
- The level of evidence on the cholesterol-lowering efficacy emerging from interventional studies in humans has been evaluated.
- The possible side effects associated with their use have been reported.
- The categories of patients who could benefit from their use have been established.