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USING NUTRACEUTICALS AND FUNCTIONAL FOODS TO MODULATE CHOLESTEROL CONCENTRATIONS

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ABSTRACT

The most important risk factor for cardiovascular disease (CVD) is an elevated circulating concentration of low-density lipoprotein (LDL-C). Therefore, lowering LDL-C concentrations is the most effective cardioprotective intervention and should be pursued by any means necessary. In this paper, we review the actions of a proper, medically-supervised use of nutraceuticals and functional foods to lower LDL-C and, consequently, CVD risk. The most effective compounds, alone or in appropriate combinations, are phytosterols, monacolin K from red yeast rice, berberine, and dietary fiber, namely beta-glucan. It is important that physicians monitor the use of nutraceuticals, verify their regular use, their effects on lipid profile, and the occurrence of untoward effects.

Future research will certainly further clarify the efficacy and mechanisms of action of the molecules described in this article, as well as their optimal use by primary care physicians and specialists.

Key words

Food supplements; functional foods; cholesterol; LDL cholesterol; cardiovascular risk; primary prevention.

Impact statement

LDL cholesterol is the major risk factor for cardiovascular disease. The use of validated nutraceuticals in otherwise low-risk patients is effective and should be oversawn by physicians.

INTRODUCTION

Life expectancy is increasing worldwide and so is the possibility to suffer from cardiovascular events in the final years. Therefore, there is an increasing need to modulate/reduce cardiovascular risk factors throughout life.

The most important risk factor for cardiovascular disease (CVD) remains an elevated circulating concentration of low-density lipoproteins (LDL). In fact, there is incontrovertible evidence that hypercholesterolemia, namely high LDL concentrations, is causally associated with atherosclerosis and its sequelae. This notion is supported by many epidemiological studies (1), controlled clinical studies (2), and Mendelian randomizations (3). Of note, no published data have been able – to date – to find a threshold value below which the correlation between plasma LDL cholesterol (LDL-C) levels and CVD risk reaches a plateau (4). The mantra 'the lower, the better' (as referred to LDL concentrations) is still valid.

In summary, lowering LDL-C concentrations is the most effective cardioprotective interven-

tion and should be pursued by any means necessary. In addition to pharmacological treatment of high-risk patients, some lifestyle interventions and proper medically supervised use of nutraceuticals and functional foods are being shown to be effective ways of modulating LDL-C and reducing cardiovascular risk. We review them in this paper.

DO PROPER DIETS AND ACTIVE LIFESTYLES EFFECTIVELY CONTROL PLASMA LDL-C?

The role of diet in cholesterol control is often overestimated by the lay public. Indeed, most studies report that commonly prescribed dietary interventions such as a reduction in cholesterol, saturated and *trans* unsaturated fatty acid intake and their replacement with polyunsaturated fatty acids modestly, that is, by - 1.5 - 5% impact LDL-C levels (5, 6). Furthermore, most patients find it difficult to fully comply with dietary guidelines or restrictions, and there is a lot of self-prescription, often following word of mouth counseling (7). The most prominent case is probably saturated fats, which do reduce plasma LDL-C levels, but do not have a great impact on CVD risk or all-cause mortality (8). In brief, current guidelines are likely to be revised in light of the most updated evidence.

Even though a balanced diet alone does not dramatically reduce cholesterolemia, its non-LDL-C mediated protective effects are not to be ignored. For example, adequate fiber intake (with its metabolic and prebiotic activity), phytochemicals such as anti-inflammatory (poly) phenols, polyunsaturated fatty acids with their anti-inflammatory, antithrombotic and antiarrhythmic actions contribute to the overall reduction in CVD risk and all-cause mortality (9). Likewise, an active lifestyle and regular physical activity do not importantly impact on cholesterol concentrations, but bring about several healthful cardiovascular effects, *e.g.* improved vascular endothelial function and vasomotion, reduced oxidative stress and inflammation, increased levels of plasma HDL-C (whose role is, however, currently being questioned), weight control, and a reduction of visceral and total body fat (11). In summary, although an active lifestyle has minor effects on LDL-C, its overall beneficial fallout reduces CVD risk (10, 11).

To summarize, a healthy lifestyle inclusive of a balanced diet reduces cardiovascular risk through various LDL-independent mechanisms and must be recommended to everyone even in the absence of hypercholesterolemia. When LDL-C levels exceed target values set by the guidelines, *e.g.* by ≥ 10%, preventive interventions should be undertaken, including the use of nutraceuticals and functional foods (12).

MOST ACTIVE FUNCTIONAL FOODS AND SUPPLEMENTS USED TO LOWER PLASMA LDL-C CONCENTRATIONS

"Nutraceuticals" are formally classified as "dietary supplements" in Europe and are often studied and prescribed in conjunction with functional foods. Their popularity in cholesterol control is growing steadily and are often used in addition to or as replacement for dietary changes and drugs such as, especially, statins (13).

At least in Europe, these products do not require prescription or medical advice to be purchased by patients. Exactly because of this, patients often self-prescribe supplements and functional foods independently without consulting their physician first. This potentially improper use of functional and nutraceutical foods could lead to adverse health effects (14, 15).

Thence, we will critically review the most frequently occurring cholesterol-lowering substances in functional foods or in supplements sold across Europe. We focus on the most popular and best studied ones, i.e. plant sterols and stanols (collectively known as phytosterols), monacolin K (as an ingredient of red yeast rice), berberine, beta-glucans, and other fibers. Our critical insight

adds to other recent publications on this subject (16-18).

Phytosterols, *i.e.* plant sterols and stanols

Plant sterols and stanols (collectively known as phytosterols) have a polycyclic chemical structure similar to that of cholesterol with the exception of the side chain linked to the cyclopentane ring (19). They are almost absent in animal-based foods, but are found (in assorted amounts) in all plant-based products (20).

Phytosterols inhibit the intestinal cholesterol absorption by competing for cholesterol in the formation of mixed micelles. Such micelles are internalized by the small intestinal absorptive enterocytes via the Niemann-Pick C1-Like 1 (NPC1L1) protein, a trans-membrane transport one. Once phytosterols are absorbed, they are secreted back – from the enterocyte into the intestinal lumen – by specific transporters (ABCG5/G8). Therefore, their plasma concentrations are usually low or very low, with the exception of individuals (1 in ~ 200,000) suffering from ABCG5/G8 mutations that cause sitosterolemia (20, 21).

Because of their direct competition with cholesterol, phytosterols inhibit its intestinal absorption. It is worth reminding that circulating cholesterol is either synthetic in nature or absorbed from the gut as derived from foods in average amounts of 300-500 mg/day, or uptaken from the bile (~ 1 gr/day). Cholesterol absorption's inhibition by phytosterols is dose-dependent and the result of the sum of food and supplements intakes. To effectively inhibit cholesterol absorption, phytosterols must be ingested in amounts that should not be lower than 1.5 gr/d. Smaller amounts are still effective, but to a much smaller degree. An example is that of Mediterranean, vegetarian and vegan diets based on plants (22). Concomitant with phytosterol-induced inhibition of intestinal cholesterol absorption, the expression of LDL receptors on the surface of hepatocytes increases as a compensatory response. Therefore, the hepatic LDL internalization also increases and their plasma concentrations, in turn, decrease (23).

Functional foods providing 1.5 to 2.0 g/day of phytosterols reduce cholesterol by about 9-10% (24). Plasma HDL-C and triglycerides levels are usually unaffected by phytosterol use. In terms of pleiotropic effects and due to their hypocholesterolemic actions, phytosterols also improve vascular endothelial function. Their effects on inflammation, as evaluated by surrogate markers, for example, C-reactive protein (CRP), are still uncertain (25, 26).

Often unbeknownst to the lay public, phytosterol-based nutraceuticals or functional foods must be taken during or immediately after the main meals to be effective. This is because cholesterol is more concentrated in the gut lumen after a meal than after a fast.This is a consequence of both the stimulation of cholesterol-rich biliary secretions and the mere presence of dietary cholesterol (27).

In terms of potential detrimental effects, regular consumption of phytosterols can reduce the absorption of some carotenoids and other fat-soluble vitamins. Hence, it is important to increase the consumption of brightly colored fruits and vegetables, usually rich in the aforementioned vitamins (23).

Monacolin K, the active component of red yeast rice

Red Yeast Rice (RYR) is the product of rice fermentation by *Monascus Purpureus* or by other members of the same fungal family. Rice (*Oryza Sativa*) fermentation by this class of fungi produces red pigments (hence, the name) along with a group of hepatic cholesterol synthesis inhibitors. Monacolin K comprises 70 to 83% of these molecules, which are found as lactones (K) and as open-ring acid conformation (Ka). Monacolin K and Ka (the active forms) are readily interconverted once ingested (28). It is worth underlying that, from a chemical viewpoint, the monacolin K structure is identical to that of lovastatin. Therefore, monacolin K efficiently inhibits HMG-CoA reductase, *i.e.* the rate-limiting enzyme in cholesterol synthesis.

Other monacolins, for example J, L, X, and M, are components of RYR and can contribute to inhibition of cholesterol synthesis, although to a much lower degree than monacolin K (28, 29). As compared with pure lovastatin in powder or tablets, RYR monacolins are more bioavailable. Consequently, they are stronger cholesterol's synthesis inhibitors than lovastatin when evaluated on a mg-per-mg basis (30). At a dosage of 3 to 10 mg/day, monacolin K lowers circulating LDL cholesterol by up to ~ 20-25%. This molecule has a minor effect on hypertriglyceridemia, but does not affect HDL-C (31).

RYR and its actions on CVD prevention have been studied in a randomized, double-blind controlled trial (RCT) performed in China. In this study, RYR extracts (xuezhikang) with an average content of 2.5-3.2 mg monacolin vs. placebo were administered to a population of approximately 5,000 elderly subjects with previous coronary events, for example, myocardial infarction (China Coronary Secondary Prevention Study). The treatment led to a 20% reduction in LDL-C levels, as compared to placebo. This cholesterol-lowering effect was also associated with a significant decrease in fatal (- 31%) and non-fatal (- 37%) coronary events, stroke (- 44%) and all-cause mortality (- 32%), over four years (32).

One of the most important issues currently affecting the use of RYR for cholesterol control is its 'natural halo'. The lay public largely believes that RYR supplements are safer compared to statins and, ergo, have fewer adverse effects. On the one hand this erroneous perception might facilitate adhesion to therapy amongst patients (33). However, RYR supplements are often perceived as substitutes of statins for individuals who are intolerant to the latter. Yet, there are only few individuals who are truly intolerant to statins and most of their reported adverse effects might be explained by a "nocebo" effect (33-35). Conclusive evidence on the actual safety of RYR is not yet available. However, because monacolin K is structurally identical to lovastatin, that is, a pharmaceutically produced statin, it is likely that patients who are really intolerant to statins should also be intolerant to RYR supplements. The higher tolerability of RYR products as compared with statins reported by some authors could be at least in part due to the low concentration of the active ingredient, *i.e.* 2.5-3 mg in most supplements. Of note, most marketed supplements contain 10 mg of monacolin K, likely due to related EFSA's approval of the claim of "maintenance of normal cholesterol values". The safety of monacolin K in doses of 10 mg as a food supplement has been re-evaluated by the EFSA (36) and has been found to be unsatisfactory.

From a pure pharmacological point of view, monacolin K is metabolized by cytochrome P450 and, in particular, by isoenzyme 3A4, which also intervenes in the metabolism of almost 30% of all medications (37). Therefore, serious pharmaceutical interactions triggered by monacolin K should not be ruled out. For instance, RYR should not be administered together with CYP3A4 strong inibitors, such as itraconazole, ketoconazole, erythromycin, clarithromycin, telithromycin, HIV protease inhibitors, cyclosporine, nefazodone, or grapefruit juice (≥ 0.2 L/day) (38). An Italian database recorded 55 adverse reactions to RYR between 2002 and 2015. Almost all the supplements at the time contained 3 mg of monacolin K (39). In particular, a case of rhabdomyolysis was observed in a patient who already suffered from rhabdomyolysis caused by a different statin, there were 10 cases of liver damage, and 19 cases of increased myalgia and/or CK, which is typical of statins. All untoward effects resolved once RYR treatment was suspended.

Although the absolute incidence of adverse effects of RYR is rather low, it is important to emphasize the need for medical supervision and avoid self-medication. Moreover, the combination of statins with RYR-based supplements should be discouraged for pharmacodynamic and untoward effects reasons. Finally, because RYR supplements are widely available online or in the supermarket, it is important

to select preparations sold by companies with high drug-standard-like industrial procedures. This will concomitantly guarantee the quality and concentration of monacolin K and avoid potential contaminations, for example, with citrinin, a nephrotoxic compound that can be found in low-quality products (29).

Dietary fiber: focus on beta-glucan

Fiber encompasses complex carbohydrates that are not digested in the human gut and therefore transit unmodified through the small intestine. High dietary intakes of fiber or their use as supplements are useful to control plasma LDL-C levels.

The mechanism(s) of action of fiber in cholesterol control is not entirely decoded, but the prevalent hypothesis points to the increase of fecal excretion of cholesterol, bile acids, and other dietary fats associated with fiber use. Viscous soluble fiber has the strongest cholesterol-lowering effect, since it absorbs water and forms a gel-like substance in the intestine (40). An example is beta-glucan ((1→3)(1→4)-β-D-glucan)), which comprises a class of non-starch polysaccharides with distinctive cholesterol-lowering properties. Beta-glucan is nondigestible and highly viscous. It is found in small concentrations in grains and cereals and some mushrooms, *e.g. Lentinus edodes* (Shiitake). However, its main dietary sources are barley and oats. Beta-glucan is also available in the supplement market as supplement and is an ingredient of some fortified functional foods (41).

Some meta-analyses have estimated the degree of beta-glucan effect on LDL-C. To summarize the results, a daily dose of 3 gr reduces LDL-C concentrations by approximately 5-6%, without significantly affecting other lipids (9). Other useful fibers are glucomannan, psyllium (a gelling polysaccharide mixture), and chitosan, which also exhibit similar effects on LDL-C (17).

In terms of cardiovascular protection, beta-glucan has interesting beneficial cardiometabolic effects, albeit at doses higher than those that reduce LDL-C. For instance, beta-glucan reduces glycemia, possibly by slowing the post-prandial uptake of glucose. Finally, beta-glucan has prebiotic effects because it selectively increases the proportion of some bacterial strains in the gut microbiota.

Berberine

Berberine is the main alkaloid extracted from the root of *B. Aristata* (and other species), an the oriental Berberis plant. It effectively controls LDL-C, which is reduced, on average, by 10-20% according to a recent meta-analysis (42). Furthermore, berberine improves plasma triglyceride, HDL-C, and blood glucose profiles (43).

Berberine possesses manifold mechanisms of action that are still undergoing basic investigation (44). Berberine may reduce levels of Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9) mRNA and, therefore, the plasma concentrations of this protein (45). On the other hand, berberine also exerts a direct effect on the LDL receptor, by stabilizing its encoding mRNA (46).

The combination of stabilization of mRNA and reduction of PCSK9 activity leads to increases in LDL receptors on the surface of liver cells and consequent increased cellular uptake of LDL, in turn decreasing plasma levels of LDL-C. As mentioned above, berberine also reduces plasma triglyceride levels, through opposite effects on MAP kinase (which is inhibited) and AMP kinase (which is enhanced). Plasma HDL-C concentrations are often moderately increased by berberine use (44).

The actions of berberine on glycemic control are rather variegated. Mechanisms of action involve the ability of berberine to reduce intestinal absorption and increase muscle and hepatic glucose uptake. Berberine exerts an incretin-like effect, that is, increases the release of GLP-1 and, hence, insulin. Further, berberine has an effect of insulin sensitization (47).

The cholesterol actions of berberine have been predominantly studied in Asian subjects; its use in the western world is quite recent. It

is noteworthy that berberine is often the component of products also containing RYR and is seldom studied alone.
When administered orally, the low bioavailability of berberine (2-3%) can produce significant differences in metabolic response. Various pharmaceutical projects are currently underway and aim at increasing berberine's intestinal absorption. Currently, berberine appears to be safe for daily intakes of 500-1,500 mg (48), but new safety studies will have to be performed on novel forulations.

Combining nutraceuticals to optimize cholesterol control

Most of the aforementioned molecules are used individually and their cholesterol-lowering effect ranges between 5 and 25%. However, the possibility exists to combine them, thereby increasing their efficacy (12).
The currently most popular combination sees the addition of berberine to supplements containing monacolin K. The rationale behind this formulation is the antagonization of the increased expression of PCSK9, which is usually associated with the administration of monacolin K and of other statins (49). Similarly, phytosterols can counteract the compensatory increase in cholesterol absorption often caused by statins (50). In short, it makes sense to merge two or more molecules active in cholesterol control, namely, in people with more pronounced dyslipidemia. As a major caveat, combination therapy should be used under strict medical supervision. In fact, it is worth re-calling that the efficacy of nutraceutical combinations on cholesterol/lipid profile must be supported by high quality studies and not simply inferred by "summing" the theoretical expected effects of individual components (**figure 1**).

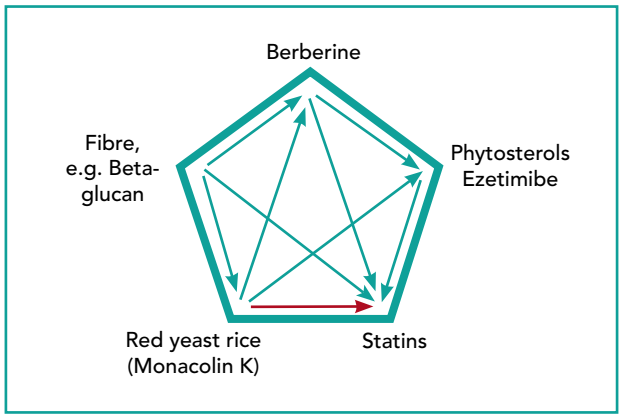

FIGURE 1. Potential associations of cholesterol-lowering substances. Blue arrows: suggested or safe associations; red arrow: discouraged association

A PHYSICIAN/PHARMACOLOGIST APPROACH TO NUTRACEUTICALS AND FUNCTIONAL FOODS FOR CHOLESTEROL CONTROL

As mentioned (vide infra), nutraceuticals and functional foods for cholesterol control are freely purchasable and often self-prescribed following word-of-mouth counselling. Therefore, it is important to note that any decision to recommend a functional food or supplement/nutraceutical is an integral part of the clinical care process and should be taken exclusively by a physician. Treatment with nutraceuticals comprises which supplement to prescribe, at which dose, and for how long. Frequent check-ups to monitor the safety and efficacy of treatment should be planned. In short, the medical management of hypercholesterolemic patients cannot be undertaken independently from the complete assessment of global cardiovascular risk (51), *e.g.* by using appropriate algorithms. Finally, the physician should provide appropriate counseling to his/her patients and inform them of the importance and role of the supplement he/she is prescribing. Adherence to the treatment is paramount.

CONCLUSIONS

There are several supplements and functional foods available on the market that effectively reduce plasma LDL-C concentrations by 5 to 25%, either when taken alone or as part of combinations. Although this represents a great opportunity to control cholesterol concentra-

tions in many low-risk individuals (as defined, for example, by the SCORE algorithm), these products are freely available for purchase and often escape the global therapeutic plans of physicians. Of note, a recent paper by Righetti et al. (52) stressed the importance of avoiding the purchase of supplements (in this case RYR) from and under-regulated and uncontrolled market, due to contaminations with *e.g.* citrinin or even simvastatin.

Another potential drawback is that of long-term compliance because patients have to sustain treatment costs over time, considering that such treatment is often lengthy and, in theory, lifelong.

It is also important for physicians to monitor the use of nutraceuticals, verify their regular use, their effects on the lipid profile, and the appearance of undesirable effects.

Future research will certainly further clarify the efficacy and mechanisms of action of the molecules described in this article, as well as their optimal use by primary care physicians and specialists.

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CONFLICT OF INTERESTS

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

All other authors declare no conflict of interests relative to this paper.

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