Editorial

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A new officially recognized role for nutraceuticals in the management of dyslipidemias for cardiovascular disease prevention and patient rehabilitation

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Despite the widespread use of nutraceuticals, physicians generally have had a low opinion of these products and have been sceptical about their benefits. However, attitudes are now changing. The European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS) have issued new guidelines for cardiovascular disease prevention and patient rehabilitation [1], which for the first time state that some nutraceuticals can be used to obtain cardiovascular benefits: 'nutraceuticals can be used either as alternatives or in addition to lipid-lowering drugs'. Such a statement would have been unthinkable a few years ago.

Guidelines generally summarize and evaluate all available evidence on a particular issue at the time of writing, with the aim of assisting health professionals to select the best management strategies for an individual patient with a given condition, taking into account the impact on outcomes as well as the risk–benefit ratio of particular diagnostic or therapeutic methods. It is not mandatory to strictly follow guidelines and recommendations, but they are intended to help health professionals take decisions in their daily practice. Nutraceuticals now have a clear role in controlling the lipidic profile of patients.

More than 4 million people in Europe (55% women, 45% men) die annually from cardiovascular disease (CVD), although cardiovascular (CV) deaths before the age of 65 are much more common in men than in women (ratio of about 5:2) [2]. Therefore, it is very important to prevent CVD by tackling unhealthy lifestyles (e.g., poor-quality diet, physical inactivity and smoking) and by reducing risk factors such as raised lipid levels and/or blood pressure. Such measures could prevent at least 80% of CVD (and 40% of cancers).

During the last two decades, innovative nutritional strategies to improve dyslipidaemia have been developed. These approaches are based on either avoiding unhealthy dietary components or encouraging the consumption of specific functional foods and/or dietary supplements, known as 'nutraceuticals'. The new ESC/EAS guidelines are the first to suggest their use, and describe their possible benefits and harms and state which of the most popular nutraceuticals are effective and which are not. The report covers phytosterols, *Monascus*-fermented rice extracts, soy proteins, water-soluble viscous fibre, policosanol and berberine.

What are known as 'phytosterols' are actually a mixture of true phytosterols, such as β-sitosterol (50–65%), campesterol (30–35%) and stigmasterol (3-5%), together with phytostanols, namely phyostanol and campestanol (together about 5%). Phytosterols occur naturally in vegetable oils and in smaller amounts in vegetables, fresh fruit, chestnuts, grains and legumes. The phytosterols used in nutraceuticals are normally extracted from the bark of *Pinus maritima* and *Pinus pinaster*. Dietary intake of plant sterols ranges from an average of 250 mg/day in Northern Europe to about 500 mg/day in Mediterranean countries. Phytosterols compete with cholesterol for intestinal absorption,

thereby modulating cholesterol levels. As food matrices do not affect and neither increase nor decrease the cholesterol-lowering ability of phytosterols, they are added to spreads and vegetable oils (functional margarine, butter and cooking oils), as well as yoghurt and other foods. The efficacy of phytosterols administered as tablets, capsules and powders is unaffected by the dosage form. Several meta-analyses show that daily consumption of 2 g of phytosterols can lower total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C) by about 10% in humans while having little or no effect on high-density lipoprotein cholesterol (HDL-C) or triglyceride (TG) levels [3]. Long-term human studies have not shown any adverse effects on health from the consumption of phytosterols.

The cholesterol-lowering effects of red yeast rice (RYR) are due to a statin-like mechanism whereby hydroxy-methyl-glutaryl-coenzyme A (HMG-CoA) reductase activity is inhibited by monacolins (the bioactive ingredient in RYR). However, there is a problem with the standardization of monacolin content in RYR products as different commercial preparations of RYR have different concentrations of monacolins, and consequently lower TC and LDL-C to different extents [4]. The quality of these products varies widely due to the differing monacolin content, the presence of cytotoxic dehydromonacolins, possible citrinin content (nephrotoxic terpene), and widespread adulteration with chemically synthetized lovastatin. Consequently, the quality of RYR products needs to be greatly improved. RYR side-effects are similar to those observed with statins and have been reported in some individuals using nutraceuticals containing RYR.

Soy proteins have been suggested to modestly lower LDL-C when used to replace animal protein. However, this needs to be further investigated as it was not confirmed when changes in other dietary components were taken into account [5].

Water-soluble viscous fibres (oat and barley β-glucan, psyllium, glucomannan and depolymerized guar gum) consistently demonstrate TC- and LDL-C lowering effects due to their ability to sequester bile salts [6]. They are well tolerated, effective and recommended for lowering LDL-C at a daily dose of at least 3 g/day. An unwanted laxative effect due to daily use of psyllium and/or glucomannan can be counteracted with the addition of depolymerized guar gum fibre.

Policosanol is a natural mixture of long-chain aliphatic alcohols extracted primarily from sugar cane wax. It is commonly used, along with other actives, in many nutraceutical products which are claimed to lower cholesterol. However, studies show that policosanol from sugar cane (as well as from rice and wheat germ) has no significant effect on cholesterol, irrespective of the dose used [7].

Berberine is an alkaloid with a clear cholesterol-lowering effect. Its mechanism of action differs from that of statins, which makes it useful in statin-intolerant patients. It also has anti-hyperglycaemic activity and so improves both the lipidic and glycaemic profile [8]. Interestingly, berberine has a greater effect in Asian than in Caucasian patients. However, a unique side-effect is its anti-diarrhoeal activity and so it must be used with caution in subjects prone to constipation.

Although some nutraceutical ingredients are considered effective for controlling cholesterol, no studies have been yet performed on subsequent impact on CVD. Nevertheless, some authors consider that a reduction in LDL-C results in CV benefits, independent of the mechanism involved [9].

In conclusion, for the very first time, an official guideline has stated that some nutraceuticals can be used to control the lipidic profile of hypercholesterolaemic subjects. However, studies have indicated that policosanol is useless because it is pharmacologically ineffective, that only low grade evidence is available for soy proteins which therefore require further research, and that RYR can be effective but products are poorly standardized and have variable quality. In contrast, phytosterols, water-soluble viscous fibres and berberine have received better reports.

Conflict of interest

Francesco Di Pierro is owner of Velleja Research.

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