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REVIEW

Management of Dyslipidemia in Individuals with Low-to-Moderate Cardiovascular Risk: Role of Nutraceuticals

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ABSTRACT

Cardiovascular diseases (CVDs) are the leading cause of premature deaths globally and in Ukraine. Dyslipidemia is a recognized risk factor for the development of CVD. Therefore, early detection and appropriate management of dyslipidemia are essential for the primary prevention of CVDs. However, currently, there is a lack of Ukraine-specific guideline recommendations focusing on the management of dyslipidemia in individuals with low-to-moderate CV risk, thus creating an urgent need for structured and easily implementable clinical recommendations/guidelines specific to the country. An expert panel of cardiologists, endocrinologists, and family physicians convened in Ukraine in March 2019. The expert panel critically reviewed and analyzed the current literature and put forth the following rec-

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ommendations for the management of dyslipidemia in individuals with low-to-moderate risk of CVDs specific to Ukraine: (1) family physicians have the greatest opportunities in carrying out primary prevention; (2) lipid-lowering interventions are essential for primary prevention as per guidelines; (3) a number of nutraceuticals and nutraceutical combinations with clinically established lipid-lowering properties can be considered for primary prevention; they also have a suggested role as an alternative therapy for statin-intolerant patients; (4) on the basis of clinical evidence, nutraceuticals are suggested by guidelines for primary prevention; (5) red yeast rice has potent CV-risk-lowering potential, in addition to lipid-lowering properties; (6) in patients with low-to-moderate cardiovascular risk, a nutraceutical combination of low-dose red yeast rice and synergic lipid-lowering compounds can be used as integral part of guideline-recommended lifestyle interventions for effective primary prevention strategy; (7) nutraceutical combination can be used in patients aged 18 to 75+ years; its use is particularly appropriate in the age group of 18–-44 years; (8) it is necessary to attract the media (websites, etc.) to increase patient awareness on the importance of primary prevention; and (9) it is necessary to legally separate nutraceuticals from dietary supplements. These consensus recommendations will help physicians in Ukraine effectively manage dyslipidemia in individuals with low-to-moderate CV risk.

Keywords: Cardiovascular diseases; Dyslipidemia; Nutraceuticals; Ukraine

Key Summary Points

Early detection and management of dyslipidemia are vital for prevention of cardiovascular diseases (CVDs) and associated premature deaths across the globe.

In Ukraine, there is a lack of specific guidelines for dyslipidemia management in individuals with low-to-moderate CV risk.

To aid physicians in Ukraine in the effective management of dyslipidemia in this population, a group of experts comprising cardiologists, endocrinologists, and family physicians convened a meeting in Ukraine in March 2019, to develop evidence-based guideline recommendations.

The expert panel emphasized the use of a combination nutraceutical with low-dose red yeast rice combined with synergic lipid-lowering compounds as a lifestyle intervention for effective primary prevention of dyslipidemia in adults with low-to-moderate CV risk.

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INTRODUCTION

Cardiovascular diseases (CVDs) are the most common cause of death globally. In 2016, 17.9 million people died as a result of CVDs, accounting for 31% of all global deaths. Among these, 85% of deaths were caused by heart attacks and strokes [1]. Globally, one-third of ischemic heart diseases occur as a result of elevated cholesterol levels. Overall, elevated cholesterol is estimated to cause 2.6 million deaths per year (4.5% of total deaths) and 29.7 million disability-adjusted life-years (DALYs), or 2.0% of total DALYs. Globally, in 2008, a total of 39% of adults (37% of men and 40% of women) had elevated total cholesterol [2].

According to the World Health Organization, noncommunicable diseases (NCDs) were estimated to account for 91% of deaths in Ukraine in 2016, of which 63% resulted from CVDs [3]. Ischemic heart disease has persistently been the top cause of death and mostly premature death in Ukraine in both 2007 and 2017 [4]. Compared to other locations, Ukraine has the highest number of premature deaths due to ischemic heart disease. Usually, CVDs are caused by a combination of risk factors, including hyperlipidemia, hypertension, diabetes, and an unhealthy diet [1]. Dietary risk is the most important factor driving the majority of deaths and disabilities in Ukraine [4].

Early detection and appropriate management of dyslipidemia are essential for the primary prevention of CVDs [1]. Guidelines recommend lifestyle interventions (collective measures including low-fat diet and physical exercise) as a primary strategy to treat dyslipidemic individuals at low-to-moderate risk. Evidence suggests that changes in lifestyle and diet can reduce the risk of coronary heart disease (CHD) by 82%. Altered nutritional practices alone can cause a 60% reduction in CHD risk [5]. The 2019 Joint ESC/EAS (European Society of Cardiology and the European Atherosclerosis Society) guidelines for the management of dyslipidemia recommend including nutraceuticals with documented lipid-lowering efficacy for the treatment of dyslipidemia as an integral part of lifestyle interventions [6].

Currently, there is a lack of guideline recommendations specific to Ukraine particularly focusing on the management of dyslipidemia in individuals with low-to-moderate CV risk, thus creating an urgent need for structured and easily implementable clinical recommendations/guidelines specific to the country. Therefore, an advisory board of leading healthcare professionals (HCPs) was held in Ukraine in March 2019 to develop consensus recommendations on the effective management of dyslipidemia with nutraceuticals in patients with low-to-moderate CV risk, as an integral part of lifestyle interventions.

METHODS

This report is based on the one-day advisory board meeting of expert professionals convened in Ukraine in March 2019. The board panelists reviewed literature evidence on dyslipidemia and associated CVDs. They discussed and debated the role of nutraceuticals in the management of dyslipidemia in individuals with low-to-moderate CV risk. The primary objectives of the advisory board meeting were to discuss:

- The need for nonpharmacological intervention as a primary prevention strategy in individuals with dyslipidemia and low-to-moderate CV risk
- Guideline recommendations on primary preventive strategies for dyslipidemia
- Differences between nutraceuticals and food supplements
- The role of a nutraceutical combination for primary prevention of CVD in individuals with low-to-moderate CV risk
- The implications of the use of a nutraceutical combination as a primary CVD-prevention strategy

This article is based on previously conducted studies and does not contain any studies with

human participants or animals performed by any of the authors.

DYSLIPIDEMIA: A CONSEQUENCE OF ABNORMAL LIPOPROTEIN METABOLISM

Low-Density Lipoprotein: The Major Atherogenic Lipoprotein

Several factors can cause CHD; dyslipidemia is one of the most important risk factors. Dyslipidemia is defined as elevated levels of total cholesterol (TC), its principal lipoprotein carrier low-density lipoprotein (LDL), triglyceride (TG), and a reduced level of high-density lipoprotein (HDL) [7]. Lipids can cause vascular damage through the induction of inflammation, oxidative stress, and immune dysregulation [5]. Although it has been validated that multiple components of serum lipids can contribute to dyslipidemia, thereby increasing the risk of CHD, the strongest evidence implicates LDL cholesterol (LDL-C) and its alternative measure, TC, as the major causative factors [7]. It has been estimated that a 1% increase in cholesterol and LDL-C increases the risk of CHD by 2–3% and 1.2–2%, respectively [5]. On the basis of compelling evidence, the National Cholesterol Education Program and the American Heart Association (AHA) have established LDL-C as the primary target for intervention for preventing CHD. Mechanistically, vascular endothelial dysfunction is initiated by elevated levels of LDL-C, which leads to atherosclerosis and coronary thrombosis [7]. An additional independent risk factor that is believed to be involved in the development of endothelial dysfunction is hyperhomocysteinemia, resulting from a diet poor in folic acid-rich food [8].

PRIMARY PREVENTION OF DYSLIPIDEMIA: FOCUS ON EARLY-STAGE APPROACH

Early Detection of Dyslipidemia: Crucial Step for Primary Prevention of CVD

Cardiovascular diseases are not commonly observed in childhood; however, CV risk factors such as dyslipidemia can be present in children, leading to CVDs in adulthood [9]. The process of atherosclerosis often begins early in life and progresses gradually for decades before resulting in clinical detection of atherosclerotic cardiovascular disease (ASCVD). Therefore, it is of significant importance to consider both intermediate- and long-term or lifetime risks while assessing the potential benefits and hazards of risk-reduction therapies [10]. Besides, the assessment of the prevalence of dyslipidemia in youth should be an integral component of any primary prevention program for CVDs [9].

Guidelines on the prevention of CVD recommend several risk-assessment systems to assess total CV risk, including Framingham models, Systemic Coronary Risk Estimation (SCORE), ASSIGN (CV risk estimation model from the Scottish Intercollegiate Guidelines Network), Q-Risk2, Prospective Cardiovascular Munster Study (PROCAM), Reynolds Risks Score, CUORE, the Pooled Cohort equations, and Globorisk. On the basis of the SCORE assessment tool, the total CV risk can be grouped into four categories [6]:

Cardiovascular risk categories as per ESC/EAS guidelines 2019 [6]	
Very high risk	People with any of the following
	Documented ASCVD, either clinical or unequivocal on imaging
	DM with target organ damage[a], or at least three major risk factors, or early onset of T1DM of long duration (> 20 years)
	Severe CKD (eGFR < 30 mL/min/1.73 m^2)
	A calculated SCORE ≥ 10% for 10-year risk of fatal CVD
	FH with ASCVD or with another major risk factor
High risk	People with
	Markedly elevated single risk factors, in particular TC > 8 mmol/L (> 310 mg/dL), LDL-C > 4.9 mmol/L (> 190 mg/dL), or BP ≥ 180/110 mmHg
	FH without other major risk factors
	DM without target organ damage[a], with DM duration ≥ 10 years or an additional risk factor
	Moderate CKD (eGFR 30–59 mL/min/1.73 m^2)
	A calculated SCORE ≥ 5% and < 10% for 10-year risk of fatal CVD
Moderate risk	Young patients (T1DM < 35 years; T2DM < 50 years) with DM duration < 10 years, without other risk factors
	Calculated SCORE ≥ 1% and < 5% for 10-year risk of fatal CVD
Low risk	Calculated SCORE < 1% for 10-year risk of fatal CVD

ASCVD atherosclerotic cardiovascular disease, *BP* blood pressure, *CKD* chronic kidney disease, *CVD* cardiovascular disease, *DM* diabetes mellitus, *eGFR* estimated glomerular filtration rate, *FH* familial hypercholesterolemia, *LDL-C* low-density lipoprotein cholesterol, *MI* myocardial infarction, *PCI* percutaneous coronary intervention, *SCORE* Systematic Coronary Risk Estimation, *T1DM* type 1 DM, *T2DM* type 2 DM, *TC* total cholesterol, *TIA* transient ischemic attack

[a] Target organ damage is defined as microalbuminuria, retinopathy, or neuropathy

Primary Prevention Strategies in Individuals with Low-to-Moderate CV Risk: What Do the Guidelines Say?

The importance of lowering LDL-C to prevent CVD is strongly emphasized in the 2019 ESC/EAS guidelines for the management of dyslipidemia, which have set LDL-C goals depending on the risk category (Table 1) [6].

Lifestyle and Dietary Interventions to Improve Lipid Profile

Lifestyle changes and drug therapies are the two available therapeutic options for lowering atherogenic cholesterol and lowering the risk of ASCVD occurrence. Among these two, lifestyle therapy is nearly universally acknowledged and considered to be the first-line therapeutic intervention necessary for dyslipidemia management among all individuals, regardless of the ASCVD risk [10]. A Cochrane review

Table 1 Recommendations for treatment goals for low-density lipoprotein cholesterol [6]

Risks strength	Recommendations	Class[a]	Level[b]
Very high	Secondary prevention	I	A
	Reduction of at least 50% from the baseline[c] LDL-C		
	LDL-C goal of < 1.4 mmol/L (< 55 mg/dL)		
	Primary prevention in individuals without FH	I	C
	Reduction of at least 50% from the baseline[c] LDL-C		
	LDL-C goal of < 1.4 mmol/L (< 55 mg/dL)		
	Primary prevention in individuals with FH	IIa	C
	Reduction of at least 50% from the baseline[c] LDL-C		
	LDL-C goal of < 1.4 mmol/L (< 55 mg/dL)		
For patients with ASCVD who experience a second vascular event within 2 years[d], LDL-C goal of < 1.0 mmol/L (< 40 mg/dL) may be considered		IIb	B
High	LDL-C goal of < 1.8 mmol/L (< 70 mg/dL) or	I	A
	Reduction of at least 50% if the baseline[c] LDL-C		
Moderate	LDL-C goal of < 2.6 mmol/L (< 100 mg/dL)	IIa	A
Low	LDL-C goal < 3.0 mmol/L (< 116 mg/dL)	IIb	A

ASCVD atherosclerotic cardiovascular disease, *FH* familial hypercholesterolemia, *LDL-C* low-density lipoprotein cholesterol

[a] Class of recommendation

[b] Level of evidence

[c] The term "baseline" refers to the LDL-C level in a person not taking any LDL-C-lowering medication. In people who are taking LDL-C-lowering medication(s), the projected baseline (untreated) LDL-C levels should be estimated on the basis of the average LDL-C-lowering efficacy of the given medication or combination of medications

[d] Not necessarily of the same type as the first event

comparing the effects of diet on cardiovascular risk parameters found a low average reduction of 0.16 mmol/L in LDL-C levels in individuals on dietary intervention vs. control individuals [11]. This study implies that to improve the modest reduction in lipid levels resulting from dietary intervention alone, it is necessary to add more interventions for significant amplification of results of dietary intervention. Although the benefits of lipid-lowering medications are clinically evident, more than 50% of patients with dyslipidemia do not undergo pharmacological treatment for two main reasons: [12]

- Pharmacological treatment is not recommended for them as per guidelines, based on their CV risk and LDL-C level.
- Pharmacological treatment is discontinued as a result of adverse events. Side effects resulting from the use of such medications have been observed.

On the other hand, dietary interventions are relatively safer and a more cost-effective choice. Therefore, an increasing number of individuals are inclined to improve their lipid profile by dietary interventions or at least by integrating dietary interventions with pharmacological treatment [12]. The role of nutrition in the prevention of CVD has been extensively studied. As advocated in many studies, dietary factors may influence atherogenesis either directly or via effects on traditional risk factors such as blood pressure, glucose levels, or plasma lipids

[6]. Although it is claimed that some dietary interventions with nutraceuticals or different food supplements improve TG and LDL-C levels by 5–20% and 10–30%, respectively, it is important to analyze the supporting evidence and assess their efficacy to suggest their use as therapeutic interventions [12].

ROLE OF NUTRACEUTICALS IN TREATMENT OF PRIMARY DYSLIPIDEMIA

Nutraceuticals vs. Food Supplements

The concept of nutraceuticals has developed and spread worldwide. In general, the use of nutraceuticals is recommended for those with a health condition who are suitable for an alternative, nonpharmacological approach [13].

The term nutraceuticals (or pharma-foods) is derived from the two words "nutrient" and "pharmaceutical," which can be a food or part of a food, as well as possessing the potential to provide medical or health benefits. The European Nutraceutical Association has defined nutraceuticals as "nutritional products that provide health and medical benefits, including the prevention and treatment of disease"; however, this definition of nutraceuticals partially overlaps that of a food supplement, mainly because both claim to be beneficial for health. A food supplement is defined as "a product developed in the form of a capsule, powder, gelcap or softgel for supplementing the diet in order to enhance health, and which contains one or more of dietary ingredients like vitamin, mineral, amino acid or other dietary or botanical substances." While the definition of food supplements is quite clear, the definition of nutraceuticals significantly overlaps and

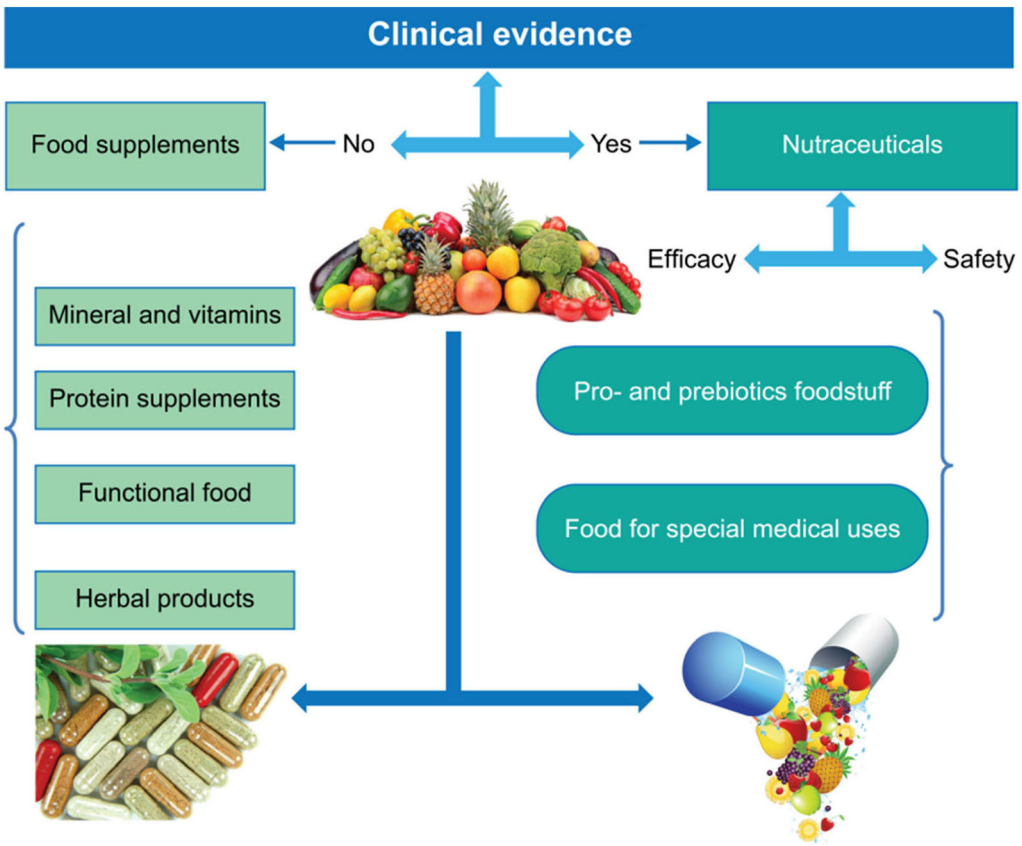

Fig. 1 Difference between food supplements and nutraceuticals [13]

Table 2 Regulation of nutraceuticals in different countries [13, 15–21]

Country	Regulation of food supplements/nutraceuticals
USA [15]	The US-FDA regulates dietary supplement products. The manufacturing and marketing firms are responsible for assessing the safety and labeling of their products, such that they meet all requirements of FDA and DSHEA regulations
Europe [16]	Food supplements are regulated by the EFSA. The EFSA performs detailed assessment of food supplements, in terms of their efficacy and safety
UK [17]	Food supplements are regulated by the foods law. In 2010, the responsibility for legislation on food supplements was transferred to the Department of Health from the Food Standards Agency
Japan [18]	The Foods for Specified Health Use (FOSHU) regulates approval of functional foods
China [19]	The SFDA regulates all affairs relating to functional foods
Canada [20]	All foods and drugs, including natural health products, are regulated by the Natural Health Products Regulations, and FDR, which are administered by Health Canada and the CFIA
India [13]	Regulated by the "Food Safety and Standards for Food for Health Supplements, Nutraceuticals, Food for Special Dietary Use, Food for Special Medical Purposes, Functional Food and Normal Food Regulations 2016," based on Sect. 22 of the FSSA
Russia [21]	Biologically active food supplement (BAFS) circulation is largely regulated by the Ministry of Health and of the Federal Service for Surveillance of Customer Rights Protection and Human Well-Being

US-FDA United States Food and Drug Administration, *DSHEA* Dietary Supplement Health and Education Act of 1994, *EFSA* European Food Safety Authority, *SFDA* State Food and Drugs Administration, *FDR* Food and Drug Regulations, *CFIA* Canadian Food Inspection Agency, *FSSA* Food Safety and Standards Act

stands between food, food supplement, and pharmaceutical. Moreover, the assessment of their potential role in medicine is quite contradictory and not unanimously shared and accepted worldwide [13, 14]. Therefore, it is strongly recommended to have a proper and univocal definition of nutraceuticals, along with a supranational shared regulation to assess the safety, efficacy, and mechanism of action of nutraceuticals based on available clinical data [14]. Figure 1 outlines the differences between food supplements and nutraceuticals, stressing the efficacy/safety requirements for these products [13, 14].

Steps to Consider When Developing a New Nutraceutical

Medicinal products have well-defined therapeutic indications, and there is a well-defined set of legislation to be followed during the production and registration of a medicinal product for marketing. Every aspect—including dose, mechanism of action, possible undesired side effects, pharmacokinetics, and method of administration—is established before a new drug can be considered for the market. Moreover, once a medicinal product is launched on the market, its benefit/risk ratio continues to be assessed throughout its entire lifespan. Nutraceuticals too should also follow such protocols. To do so, the first step is to assess therapeutic efficacy based on positive evidence from clinical data. This step should include contributions from different professionals with wide expertise, ranging from food chemistry and food safety to structure–activity studies, to assess the mechanism of action, nutritional aspects, pharmacology, pharmacokinetics, and pharmacodynamics of each nutraceutical [13]. Given the fact that nutraceuticals are beneficial for health, they can be considered safe or generally recognized as safe (GRAS). However, the

safety of nutraceuticals is of the utmost concern, since they can be contaminated with inorganic and organic material that could cause health issues [14]. Moreover, any possible interactions between food and/or drugs assumed together with nutraceuticals should not be underestimated. Therefore, these claims regarding potential medical benefits and safety of nutraceuticals must be substantiated by clinical data [13]. Different countries have legislative authorities for regulating the development, manufacturing, and marketing of nutraceuticals or food supplements (Table 2) [13, 15–21].

With the availability of nutraceuticals, which are clinically documented for safety and efficacy in lowering LDL-C, the gap between the "nonpharmacological" and the "pharmacological interventions" can be filled.

Table 3 Impact of specific lifestyle changes on lipid levels [6]

Lifestyle interventions to reduce TC and LDL-C levels	Magnitude of effect[a]	Level of evidence[b]
Avoid dietary trans fats	++	A
Reduce dietary saturated fats	++	A
Increase dietary fiber	++	A
Use functional foods enriched with phytosterols	++	A
Use red yeast rice nutraceuticals	++	A
Reduce excessive body weight	++	A
Reduce dietary cholesterol	+	B
Increase habitual physical activity	+	B

TC total cholesterol, *LDL-C* low-density lipoprotein cholesterol

[a] ++ magnitude of effect 5–10%,+ magnitude of effect < 5%

[b] Level of evidence refers to the impact of each dietary modification on plasma levels of a specific lipoprotein class

Nutraceuticals as an Integral Part of Lifestyle Interventions

The evidence on lifestyle interventions in patients with CV risk is compelling; however, the efficacy of lifestyle interventions is often limited by factors such as poor adherence to treatment in the medium-to-long run [22]. Therefore, the 2019 ESC guideline recommendations included innovative nutritional strategies to cope with dyslipidemia that envisage either changing a few "risky" dietary components or encouraging the consumption of "healthy" functional foods and/or dietary supplements [6].

In this context, it is important to mention that potential cholesterol-lowering activity is present in some dietary components in small amounts of food. This has led to a spur in the use of nutraceuticals, which contain specific ingredients in well-defined amounts, in recent years. The evaluation of such functional foods depends not only on the clinical evidence of beneficial effects to improve health or lower the risk of the disease but also on tolerability and the absence of undesirable side effects. The validation of health claims specific to each food should be based on results from interventional studies. The influence of lifestyle changes and functional foods (nutraceuticals) on the lipid profile is summarized in Table 3 [6].

Nutraceuticals are agents between nutrients and drugs that can be used as supplements. The inclusion of nutraceuticals in the diet is needed for lifestyle diseases such as hypercholesterolemia, obesity, and hypertension. Since nutraceuticals can be considered beyond the diet to prevent the onset of such diseases and before drugs to treat diseases, nutraceuticals can be considered as agents to be used 'beyond the diet but before the drugs' [23]. Therefore, nutraceuticals are perceived as pharma-foods, since they are closer to pharmaceuticals owing to their clinically proven efficacy in specific pathological conditions. They help in combating major health issues, such as CVD, metabolic syndrome, diabetes, osteoporosis, and hypercholesterolemia [24]. The possible role of nutraceuticals in the prevention and treatment of pathological and chronic diseases, especially

in patients who do not qualify for pharmacological therapy, indicates that these food supplements can be used in the future for both prevention and therapy for certain chronic conditions. However, the big challenge in this context would be to improve their bioavailability and clearly define their mechanism of action [25].

More than 40 lipid-lowering nutraceuticals have been studied that have proven benefits on lipid metabolism and positively affect CV health. Results from both preclinical and clinical trials validate their use for everyday management of dyslipidemia [26]. Given the lack of effective therapy for lipid disorders, nutraceuticals seem to be a worthwhile alternative to conventional lipid-lowering therapy for at-risk patients who do not reach LDL-C goals. Among common nutraceuticals, red yeast rice and spirulina are the most potent in lowering total LDL-C (up to 35–40 mg/dL). Evidence from clinical studies indicates that the nutraceuticals are safe and generally well tolerated even at high doses [27]. Moreover, since the lipid-lowering effect of nutraceuticals is exerted through multiple mechanisms, it makes them potent candidates for use in combination products containing conventional lipid-lowering drugs. Additionally, some nutraceuticals are well tolerated in statin-intolerant patients, thereby serving as an important alternative to conventional lipid-lowering therapy [27].

Statins are the most common drugs used in patients with CVD, owing to their high effectiveness in lowering primary and secondary CV endpoints and reducing LDL-C levels. However, often as a result of exaggerated toxicity-related concerns, use of statin therapy is discontinued, which is also referred to as statin intolerance. In this context, it has been suggested that certain nutraceuticals, either alone or in combination, might be considered as an alternative to statin therapy. The first set of recommendations on the management of statin intolerance with nutraceuticals suggests that they can be used either alone or in combination for high-risk or very high-risk patients with partial or complete statin intolerance who cannot reach target LDL-C levels with other therapies and for patients with high cholesterol levels and other risk factors who are at intermediate CV risk with the use of statin therapy [28]. Accumulating clinical evidence, including randomized controlled trials and meta-analyses, has assessed the lipid-lowering efficacy of different nutraceuticals, as discussed below.

A meta-analysis of 124 randomized controlled trials revealed that there is a clear dose–response effect of plant sterols and stanols in lowering LDL-C between 6% and 12% [29]. A meta-analysis of 11 randomized controlled trials involving 874 people with hypercholesterolemia and/or type 2 diabetes observed that berberine positively affected the plasma lipid profile by increasing HDL-C (+ 0.05 mmol/L, 95% CI 0.02–0.09) and decreasing LDL-C (− 0.65 mmol/L, 95% CI − 0.76 to − 0.54), TC (− 0.61 mmol/L, 95% CI − 0.83 to − 0.39), and TG (− 0.50 mmol/L, 95% CI − 0.69 to − 0.31) [30]. A meta-analysis of 17 randomized clinical trials involving 916 patients with hypercholesterolemia reported that β-glucan significantly decreased LDL-C (− 0.21 mmol/L, 95% CI 0.27 to − 0.14; $p < 0.00001$) [31]. In a meta-analysis of 14 randomized controlled trials involving 531 patients, as compared to placebo, glucomannan significantly reduced TG, TC, and LDL-C by a weighted mean difference (WMD) of − 11.08 mg/dL (95% CI − 22.07, − 0.09), − 19.28 mg/dL (95% CI − 24.30, − 14.26), and − 15.99 mg/dL (95% CI − 21.31, − 10.67), respectively [32]. A meta-analysis of 35 randomized controlled trials including 2670 subjects concluded that soy proteins significantly reduce LDL-C by − 4.83 (95% CI − 7.34, − 2.31) mg/dL, TG by − 4.92 (95% CI − 7.79, − 2.04) mg/dL, and TC by − 5.33 (95% CI − 8.35, − 2.30) mg/dL—in addition to increasing HDL-C by 1.40 (95% CI 0.58, 2.23) mg/dL [33].

A systematic review and meta-analysis found that red yeast rice preparations reduce TG, LDL-C, and TC by WMD − 20.23 mmol/L (95% CI − 20.31, − 20.14; $p < 0.001$), − 20.87 mmol/L (95% CI − 21.03, − 20.71; $p < 0.001$), and − 20.97 mmol/L (95% CI − 21.13, − 20.80; $p < 0.001$), respectively [34]. In statin-intolerant subjects, 24-week treatment with red yeast rice reduced TG by a mean percentage difference of − 20.0% (95% CI − 38.9 to − 1.1), LDL-C by

− 21.6% (95% CI − 29.4 to − 13.8), and TC by − 16.7% (95% CI − 23.4 to − 10.3) [35]. In addition to lipid-lowering effects, the effects of red yeast rice on CV outcomes have also been evaluated [36]. In patients with a history of hypercholesterolemia and acute myocardial infarction, long-term supplementation with red yeast rice reduces coronary death by 29.2%, all-cause mortality by 36.3%, and the relative risk of major coronary events by 38.2% [37].

The lipid-lowering effect of red yeast rice can be attributed to monacolin K, a component whose structure in lactone form is identical to that of lovastatin. Therefore, when administered in doses similar to therapeutic doses of lovastatin, significant safety concerns could be associated with the use of monacolin K [38]. A few concerns had been raised regarding the safety of red yeast rice, based on a few toxicity reports. Therefore, Fogacci et al. conducted a meta-analysis of safety data from 53 randomized controlled trials conducted among a total of 8535 subjects: 4437 in the red yeast rice arm and 4303 in the control arm. Some patients had prematurely terminated the trial due to reasons independent of the tested nutraceuticals, so the meta-analysis was performed on 8535 subjects. While the primary outcome was musculoskeletal disorders (MuD), non-musculoskeletal adverse events (Non-MuD) and serious adverse events (SAE) were the secondary outcomes of the meta-analysis. The study revealed that monacolin K did not increase the risk of MuD (odds ratio [OR] 0.94, 95% CI 0.53, 1.65), lowered the risk of SAE (OR 0.54, 95% CI 0.46, 0.64) and non-MuD (OR 0.59, 95% CI 0.50, 0.69), as compared to control. Moreover, a negative association was observed between an increasing daily dose of monacolin K and an increasing risk of non-MuD (slope − 0.10, 95% CI − 0.17, − 0.03; two-tailed $p < 0.01$). Therefore, this study established the overall safety and tolerability of red yeast rice as a lipid-lowering dietary supplement in a large population of subjects with moderate hypercholesterolemia [39].

Recently, most nutraceuticals with lipid-lowering functions have been commercialized as a combination of two or more substances, lowering the dosages of single components and thereby reducing the risk of side effects. Moreover, such a combination exerts a cumulative effect of individual components that act on lipid metabolism with different mechanisms. For example, while substances such as soluble fibers, glucomannan, and plant sterols can lower lipid and biliary salt absorption by the bowel, other nutraceuticals such as berberine and soybean proteins can enhance the hepatic uptake of cholesterol. Again, some nutraceuticals such as berberine, soy protein, and chlorogenic acid can induce LDL-C excretion, while others such as monacolins, policosanols, allicin from garlic, and bergamot reduce the hepatic synthesis of cholesterol by inhibiting β-hydroxy-β-methyl-glutamyl coenzyme A (HMG-CoA) reductase enzyme. Additionally, some nutraceuticals such as chlorogenic acid and green coffee can reduce the oxidation of the LDL or increase thermogenesis and lipid metabolism. Therefore, in patients with slightly elevated cholesterol levels, low CV risk, or those who are intolerant to pharmacological therapy, a combination of lipid-lowering nutraceuticals may be a potential alternative to the use of drugs [16, 17].

Accumulating evidence reporting the cholesterol-lowering potential of various nutraceuticals has attracted significant interest from experts and encouraged the development of multicomponent novel nutraceuticals. This development is driven by the notion that nutraceutical combinations will help achieve a cumulatively large reduction in total and LDL cholesterol levels. The development of nutraceutical combinations is based on two main speculative assumptions: (i) complementary lipid-lowering effects of each of the components of the nutraceutical combination; and (ii) lowering the effective doses of individual components to ensure tolerability along with maintenance of optimum lipid-lowering efficacy. A few studies have reported the slightly higher cholesterol-lowering effect of nutraceutical combinations vs. their individual components [15]. Such nutraceutical combinations include (1) red yeast rice and policosanols, (2) red yeast rice, policosanols, and berberine, (3) red yeast rice and plant sterols, (4) red yeast rice and artichoke, (5) red yeast rice, policosanol, and silymarin, (6) red yeast rice and

antioxidants, (7) berberine with bioactive lipid-lowering agents other than red yeast rice, and (8) soy protein and plant sterols [36].

The combination of phytochemical nutraceuticals has been found to positively modulate lipid metabolism in hypercholesterolemic patients and positively affect CV health. However, even under such conditions, it is important to focus on the individual components, to take full advantage of their potential and features [26].

EU GUIDELINE-BASED NUTRACEUTICAL: ROLE IN MANAGEMENT OF DYSLIPIDEMIA

Composition of the Nutraceutical

The use of novel nutritive strategies based on the consumption of nutraceuticals or "healthy" functional foods and/or dietary supplements, either as an alternative or as an addition to drug therapy, has been suggested by the 2019 ESC/EAS guidelines for the management of dyslipidemia. The following nutraceuticals with lipid-lowering effects were reported by the 2019 ESC/EAS guidelines for the management of low-to-moderate dyslipidemia: red yeast rice, dietary fiber, soy protein, phytosterols, berberine, and n-3 unsaturated fatty acids [6].

In the context of the use of nutraceuticals for controlling dyslipidemia, the potential candidature of a particular nutraceutical combination has been identified for the management of dyslipidemia in subjects with low-to-moderate CV risk. The chief constituents of this nutraceutical combination are as follows [40]:

- Red yeast rice: 200 mg (~ 3 mg of monacolin K)
- Policosanol: 10 mg
- Folic acid: 0.2 mg
- Coenzyme Q_{10}: 2 mg
- Astaxanthin: 0.5 mg

Among these components of the nutraceutical combination, lipid-lowering functions are primarily attributed to monacolin K and policosanol. Monacolin K, the active component of red yeast rice (*Monascus purpureus*), works via a statin-like mechanism. It competitively inhibits the activity of HMG-CoA reductase, a key enzyme in cholesterol biosynthesis. Policosanol, on the other hand, inhibits the synthesis of HMG-CoA reductase [8]. Furthermore, the combined effects of monacolins and policosanol decrease intracellular cholesterol levels, which triggers the upregulation of transcription of the low-density lipoprotein receptor (*LDLR*) gene resulting in enhanced expression of *LDLR* in liver cells and improving the clearance of LDL cholesterol from the circulation. Coenzyme Q_{10} and astaxanthin are the antioxidant components of the nutraceutical combination that may reduce the transformation of lipoproteins into proatherogenic molecules by preventing LDL peroxidation. Folic acid remethylates homocysteine to methionine leading to reduced homocysteine plasma levels, thereby potentially lowering the CV risk [40].

Scientific Rationale for the Nutraceutical Combination

Although most components of nutraceutical combinations have individual lipid-lowering effects, the use of a combination of nutraceuticals is more beneficial, since such combinations contain lipid-lowering ingredients at subclinical doses, such that the overall lipid-lowering efficacy of each component is increased through synergy. Also, there are fewer side effects owing to the use of a lowered effective dose of individual components, and the combination hits multiple targets [26]. The clinical development of a nutraceutical within a pharmaceutical company necessitates an extremely rigorous approach, with the following criteria: maintenance of the highest quality-control standards, i.e., eliminating the risk of toxic contaminants in the natural components, along with pharmacokinetic studies to confirm the bioavailability and to eliminate potential risks for drug–drug interactions [8, 13]. Therefore, as the use of nutraceuticals has been on the rise, there has been increased demand for pharmacokinetic studies to understand their bioavailability

and also exclude any possibility of drug–drug interactions. Unfortunately, strong pharmacokinetic data are often lacking for several nutraceuticals. Therefore, clinical studies concerning nutraceuticals as pharma-foods or any interactions between foods and/or drugs with nutraceuticals have been highlighted as an essential requirement [13].

In one pharmacokinetic study, a rigorous, single-center, open-label randomized trial was performed on a nutraceutical containing monacolin K. The study comprised 12 healthy male volunteers (aged 18–45 years) who were administered the nutraceutical formulation to study the plasma concentrations of monacolin K and its metabolite, lovastatin hydroxy acid, at different time points post treatment. The study revealed that monacolin K was absorbed with peak plasma concentrations at 2.5 h post dosing at an average value of 3.06 ng/mL. This is the first study that investigated the pharmacokinetics of a monacolin K-containing nutraceutical [40, 41]. The second pharmacokinetic study investigated the potential of any clinically relevant inhibition of the CYP (cytochrome P450) enzyme system, after single-dose administration of the aforementioned nutraceutical combination. The study comprised 12 healthy male volunteers (aged 20–43) enrolled in a single-center, open-label, randomized, crossover clinical study, and the subjects were randomized either to (1) a cocktail of drugs, including 100 mg caffeine, 20 mg omeprazole, 100 mg metoprolol, 0.03 mg/kg midazolam, and 10 mg warfarin, metabolized through the same cytochrome system, as used by the liver to metabolize the nutraceutical components; or to (2) the same drug cocktail along with one tablet of the nutraceutical. The study revealed that when the nutraceutical is administered in combination at the recommended dose, there is no clinically relevant inhibition of the activity of the CYP isoenzymes [40, 42].

Randomized controlled trials have been conducted to study the effects of nutraceutical combinations along with diet modification, mostly in subjects with dyslipidemia and low-to-moderate CV risk. Such trials not only revealed the excellent safety and tolerability of nutraceutical combinations but they also found that nutraceutical combinations were an effective alternative to lipid-lowering treatment, viz. statins. These findings also support the fact that low doses of the active ingredients of the nutraceutical combination were low enough not to be associated with undesirable effects, but were high enough to exert therapeutic benefits [40].

Clinical Experience with the Nutraceutical Combination

The nutraceutical combination discussed above is associated with significant improvement in the lipid profile, as visible from 6 weeks of treatment and maintained for up to 6 months, as observed in long-term studies [40]. Multiple trials have been performed on this nutraceutical combination to study its efficacy and safety.

A single-center, randomized, double-blind, placebo-controlled trial was conducted in Germany between July 2014 and May 2015. All the 142 male and female participants with raised cholesterol were randomly assigned into two groups of treatment: (1) nutraceutical combination or (2) placebo group. The endpoint of the study was to monitor the reduction of LDL-C levels in the nutraceutical combination vs.

Table 4 Reduction in TC and LDL-C after 16 weeks of both interventions [3]

Age group	Reduction in TC (%)		Reduction in LDL-C (%)	
	Nutraceutical plus diet	Diet alone	Nutraceutical plus diet	Diet alone
Adults	17.3*	10.5	18.1*	8.7
Elderly	17.4*	9.6	18.1*	8.1

*$p < 0.001$ vs. diet alone

placebo over the study duration of 12 weeks. The results revealed that the relatively lower content of monacolin K (3 mg/day), folic acid (0.2 mg), coenzyme Q_{10} (2 mg), and astaxanthin (0.5 mg) in combination significantly reduced LDL-C (14.8%), TC (11.2%), and homocysteine (12.5%) ($p < 0.001$ for all parameters) after 12 weeks. This study indicated that the nutraceutical combination is effective in lowering cholesterol and homocysteine and that it can be integrated into primary CV disease-prevention strategies [43].

Another single-center, randomized, diet-controlled trial was performed in Greece in 80 subjects with hypercholesterolemia for whom drug therapy was not indicated. The study was conducted over a 6-month intervention period, and all the participants were randomly assigned in two groups (1:1 ratio): (i) to receive the nutraceutical combination in addition to a healthy diet or (ii) to adhere only to a healthy diet. The study demonstrated that the administration of the nutraceutical combination, together with a healthy diet for 6 months, significantly improved the lipid profile in subjects with primary dyslipidemia for whom drug therapy is not indicated. After 6 months of follow-up, patients who received the nutraceutical combination had a statistically significant decrease in TC and LDL-C level: 240.5 ± 31.4 to 211.7 ± 13.5 ($p < 0.001$) and 166.4 ± 29.6 to 143.9 ± 17.9 ($p = 0.052$), respectively [44].

A multicenter, real-life, diet-controlled, non-interventional trial was conducted in Italy to study the efficacy of the nutraceutical combination. In this randomized, multicenter study, 411 Italian primary care units ($n = 2408$) compared the efficacy of the nutraceutical combination plus diet vs. diet alone for 16 weeks in subjects with hyperlipidemia (TC > 200 mg/dL or LDL-C > 150 mg/dL). The study included only those individuals for whom a specific drug therapy (e.g., statins) was either not (yet) necessary or not well-tolerated or contraindicated. The study revealed that the reduction in TC and LDL-C was significantly higher in the nutraceutical plus diet group vs. diet-alone group (Table 4). This effect was uniformly observed in all subjects independent of age classes and administration time during the day, thereby supporting the potential candidature of nutraceutical for controlling hypercholesterolemia with a positive impact on CV disease prevention in all categories of subjects [45].

PANEL'S RECOMMENDATION

During the advisory board meeting, the evidence-based discussion revealed that dyslipidemia is an important and independent risk factor for CVD and that various international guidelines recommend lifestyle and dietary changes as a primary preventive measure for the treatment of low-to-moderate dyslipidemia. The 2019 ESC/EAS guidelines for the management of low-to-moderate dyslipidemia recommend including nutraceuticals as an integral part of lifestyle and dietary modification. The key points of the discussion were (1) family physicians have the most crucial role in primary prevention; (2) lipid-lowering interventions are essential for primary prevention as per guidelines; (3) a number of nutraceuticals and nutraceutical combinations with clinically established lipid-lowering properties can be considered for primary prevention; they also have a suggested role as an alternative therapy for statin-intolerant patients; (4) on the basis of clinical evidence, nutraceuticals are suggested by guidelines for primary prevention; (5) red yeast rice has potent CV-risk-lowering potential, in addition to lipid-lowering properties; (6) in patients with low-to-moderate cardiovascular risk, a nutraceutical combination of low-dose red yeast rice and synergic lipid-lowering compounds can be used as integral part of guideline-recommended lifestyle interventions for effective primary preventive; (7) the nutraceutical combination can be used in patients aged 18 to 75+ years; its use is particularly appropriate in the age group of 18–44 years; (8) it is necessary to attract the media (websites, etc.) to increase patient awareness on the importance of primary prevention; and (9) it is necessary to legally separate nutraceuticals from dietary supplements.

The panelists came up with the following recommendations specific to Ukraine:

1. Family physicians have the most crucial role and the greatest opportunities

incarrying out primary prevention. It is necessary to use a questionnaire (to assess-cardiovascular risk) that patients can fill out while waiting for a doctor's appointment.(High recommendation)
2. For primary prevention in patients with low-to-moderate cardiovascular risk,nutraceutical combinations can be used (in association with lifestyle changes,including dietary measures and physical exercise) in all age groups. Althoughnutraceutical combinations can be used in patients aged 18 to 75+ years, their use isparticularly appropriate in the age group of 18–44 years. (High recommendation)
3. It is necessary to attract the media (websites, etc.) to increase patient awareness onthe importance of primary prevention. (High recommendation)
4. It is necessary to legally separate nutraceuticals from dietary supplements. (Highrecommendation)

DISCUSSION

The high incidence of CV diseases highlights the need to address risk factors, particularly dyslipidemia [26]. As per different national and international guidelines, the chief preventive approach for combating CV diseases is a healthy lifestyle, supported (when specifically recommended on the basis of the CV risk) by pharmacotherapy [46].

Lifestyle modification acts as the cornerstone of treatment for patients with low-to-moderate dyslipidemia. For patients who are at low-to-moderate CV risk, lifestyle interventions—including the use of a lipid-lowering nutraceutical—should be given an adequate trial for at least 3 months before considering drug therapy [10].

Significant evidence is available to link the use of dietary compounds and reduction in CVDs [46]. Several studies have elucidated the role of nutraceuticals in controlling dyslipidemia or in the reduction of vascular markers such as plaque progression, coronary artery calcium score, carotid intima-media thickening and obstruction, endothelial function, and generalized atherosclerosis. The combined implementation of scientifically proven nutraceuticals and a lipid-lowering diet reduces LDL-C, lowers LDL particle number, and increases their size—thereby reducing atherosclerosis and CVD [5]. For these reasons, the use of nutraceuticals in correcting dyslipidemia is gaining popularity [45].

Multiple individual natural ingredients with cholesterol-lowering effects have been identified. However, evidence indicates that the use of a combination of these compounds in a single, well-characterized nutraceutical formulation yields additive (or synergistic) efficacy. Similar results have also been obtained when nutraceuticals are combined with lipid-lowering drugs, leading to the improvement of CV health [26]. Owing to such positive health benefits, novel nutraceuticals are being developed continuously and have quickly spread worldwide [13]. The 2019 joint ESC/EAS guidelines for the management of dyslipidemia recommend nutraceuticals containing purified red yeast rice in people with hyperlipidemia who do not qualify for treatment with statins, considering their CV risk [6].

Although several nutraceuticals that claim to offer cholesterol-lowering effects are currently commercially available, their efficacy is often questionable. The first and foremost concern while selecting a nutraceutical is the absence of a guarantee of good manufacturing practice (GMP), similar to the ones followed for drug production, for assuring a quality product with a standardized composition. This is a critically important issue; since most ingredients are extracted from natural sources, it is essential to prove their purity. Nutraceuticals developed within a pharmaceutical company, under GMP procedures, should thus be preferred. Secondly, often solid clinical data validating their cholesterol-lowering claims and supporting their efficacy and safety are lacking for these products. Therefore, the availability of a clinically tested lipid-lowering nutraceutical could be very useful, especially for patients with low-to-medium CV risk. In this scenario, a patented nutraceutical combination containing red yeast rice extract, policosanols, folic acid,

coenzyme Q_{10}, and astaxanthin has been developed within the aforementioned pharmaceutical environment with implemented GMP procedures to control hypercholesterolemia, homocysteinemia, and free radicals [45].

CONCLUSIONS

Nutraceutical combinations along with a healthy diet and lifestyle modification could be used as a potentially effective approach for the primary prevention and treatment of dyslipidemia in subjects with low-to-moderate CV risk for whom drug therapy is not initially recommended by guidelines.

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REFERENCES

1. World Health Organization. Cardiovascular diseases (CVDs). https://www.who.int/en/news-room/fact-sheets/detail/cardiovascular-diseases-(cvds). Accessed 9 July 2019.
2. World Health Organization. Raised cholesterol. https://www.who.int/gho/ncd/risk_factors/cholesterol_text/en/. Accessed 9 July 2019.
3. World Health Organization. Noncommunicable diseases (NCD) country profiles. 2018. https://www.who.int/nmh/countries/ukr_en.pdf. Accessed 9 July 2019.
4. Ukraine Institute for Health Metrics and Evaluation. https://www.healthdata.org/ukraine. Accessed 9 July 2019.
5. Kota SK, Jammula S, Kota SK, et al. Nutraceuticals in dyslipidemia management. J Med Nutr Nutraceut. 2013;2(1):26–40.
6. Mach F, Baigent C, Catapano AL, et al. 2019 ESC/EAS guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. Eur Heart J. 2020;41:111–88.
7. Leon SA, Bronas UG. Dyslipidemia and risk of coronary heart disease: role of lifestyle approaches for its management. Am J Lifestyle Med. 2009;3:257–73.
8. Barrios V, Escobar C, Cicero AF, et al. A nutraceutical approach (Armolipid Plus) to reduce total and LDL cholesterol in individuals with mild to moderate dyslipidemia: review of the clinical evidence. Atheroscler Suppl. 2017;24:1–15.
9. Nepal G, Tuladhar ET, Acharya K, et al. Dyslipidemia and associated cardiovascular risk factors among young Nepalese university students. Cureus. 2018;10:e2089. https://doi.org/10.7759/cureus.2089.
10. Jacobson TA, Ito MK, Maki KC, et al. National lipid association recommendations for patient-centered management of dyslipidemia: Part 1—full report. J Clin Lipidol. 2015;9:129–69.
11. Rees K, Hartley L, Flowers N, et al. 'Mediterranean' dietary pattern for the primary prevention of cardiovascular disease. Cochrane Database Syst Rev. 2013;8:CD009825.
12. Huang J, Frohlich J, Ignaszewski AP. The impact of dietary changes and dietary supplements on lipid profile. Can J Cardiol. 2011;27:488–505.
13. Santini A, Cammarata SM, Capone G, et al. Nutraceuticals: opening the debate for a regulatory framework. Br J Clin Pharmacol. 2018;84:659–72.
14. Santini A, Novellino E. Nutraceuticals—shedding light on the grey area between pharmaceuticals and food. Expert Rev Clin Pharmacol. 2018;11(6):545–7.
15. The US-Food and Drug Administration. Dietary supplements. https://www.fda.gov/food/dietary-supplements. Accessed 20 Aug 2020.
16. European Food Safety Authority. Food supplements. https://www.efsa.europa.eu/en/topics/topic/food-supplements. Accessed 20 Aug 2020.
17. GOV.UK. Guidance: food supplement use and labels. https://www.gov.uk/government/publications/food-supplements-guidance-and-faqs. Accessed 20 Aug 2020.

18. Shimizu T. Health claims on functional foods: the Japanese regulations and an international comparison. Nutr Res Rev. 2003;16(2):241–52.

19. Yang Y. Scientific substantiation of functional food health claims in China. J Nutr. 1199S;138(6): 1199S–S1205205.

20. Labbe MR, Dumais L, Chao E, et al. Health claims on foods in Canada. J Nutr. 1221S;138:1221S–7S. https://doi.org/10.1093/jn/138.6.1221S.

21. Tutelyan V, Sukhanov B, Kochetkova A, et al. Russian regulations on nutraceuticals, functional foods, and foods for special dietary uses. In: Bagchi D, editor. Nutraceutical and functional food regulations in the United States and around the world. London: Academic; 2019. p. 399–416.https://doi.org/10.1016/B978-0-12-816467-9.00026-5.

22. Pirro M, Vetrani C, Bianchi C, Mannarino MR, Bernini F, Rivellese AA. Joint position statement on "Nutraceuticals for the treatment of hypercholesterolemia" of the Italian Society of Diabetology (SID) and of the Italian Society for the Study of Arteriosclerosis (SISA). Nutr Metab Cardiovasc Dis. 2017;27:2–17.

23. Santini A, Novellino E. Nutraceuticals: beyond the diet before the drugs. Curr Bioact Compd. 2014;10: 1–12.

24. Santini A, Novellino E. Nutraceuticals in hypercholesterolaemia: an overview. Br J Pharmacol. 2017;174(11):1450–63.

25. Durazzo A, Lucarini M, Santini A. Nutraceuticals in human health. Foods. 2020;9:370. https://doi.org/10.3390/foods9030370.

26. Cicero AF, Colletti A. Combinations of phytomedicines with different lipid lowering activity for dyslipidemia management: the available clinical data. Phytomedicine. 2016;23:1113–8.

27. Sahebkar A, Serban MC, Gluba-Brzózka A, et al. Lipid-modifying effects of nutraceuticals: an evidence-based approach. Nutrition. 2016;32(11–12): 1179–92.

28. Banach M, Patti AM, Giglio RV, et al. The role of nutraceuticals in statin intolerant patients. J Am Coll Cardiol. 2018;72(1):96–118.

29. Ras RT, Geleijnse JM, Trautwein EA. LDL-cholesterol-lowering effect of plant sterols and stanols across different dose ranges: a meta-analysis of randomised controlled studies. Br J Nutr. 2014;112(2):214–9.

30. Dong H, Zhao Y, Zhao L, et al. The effects of berberine on blood lipids: a systemic review and meta-analysis of randomized controlled trials. Planta Med. 2013;79(6):437–46.

31. Zhu X, Sun X, Wang M, et al. Quantitative assessment of the effects of beta-glucan consumption on serum lipid profile and glucose level in hypercholesterolemic subjects. Nutr Metab Cardiovasc Dis. 2015;25(8):714–23.

32. Sood N, Baker WL, Coleman CI. Effect of glucomannan on plasma lipid and glucose concentrations, body weight, and blood pressure: systematic review and meta-analysis. Am J Clin Nutr. 2008;88(4):1167–75.

33. Tokede OA, Onabanjo TA, Yansane A, et al. Soya products and serum lipids: a meta-analysis of randomised controlled trials. Br J Nutr. 2015;114(6): 831–43.

34. Li Y, Jiang L, Jia Z, et al. A meta-analysis of red yeast rice: an effective and relatively safe alternative approach for dyslipidemia. PLoS One. 2014;9(6): e98611.

35. Chung VC, Liu S, Sit RW. Is red yeast rice capsule beneficial for treating dyslipidemia amongst statin-intolerant patients as compared to placebo? Adv Integr Med. 2014;1(3):151–2.

36. Cicero AFG, Colletti A, Bajraktari G, et al. Lipid-lowering nutraceuticals in clinical practice: position paper from an International Lipid Expert Panel. Nutr Rev. 2017;75(9):731–67.

37. Li JJ, Lu ZL, Kou WR, et al. Beneficial impact of Xuezhikang on cardiovascular events and mortality in elderly hypertensive patients with previous myocardial infarction from the China Coronary Secondary Prevention Study (CCSPS). J Clin Pharmacol. 2009;49(8):947–56.

38. EFSA Panel on Food Additives, and Nutrient Sources added to Food (ANS), Younes M, Aggett P, et al. Scientific opinion on the safety of monacolins in red yeast rice. EFSA J. 2018;16(8):e05368.

39. Fogacci F, Banach M, Mikhailidis DP, et al. Safety of red yeast rice supplementation: a systematic review and meta-analysis of randomized controlled trials. Pharmacol Res. 2019;143:1–16.

40. Armolipid Product Monograph. Mylan (Mylan data on file). 2019.

41. Persiani S, Sala F, Zangarini M, et al. Effect of food on the oral bioavailability of berberine and monacolin administered in combination in healthy male volunteers. J Pharm Pharmacol. 2014;2:703–12.

42. Persiani S, Sala F, Manzotti C, et al. Effect of a combination of berberine and monacolin on CYP

enzymes: an oral cocktail interaction study in healthy volunteers. J Pharm Pharmacol. 2014;2: 660–8.

43. Heinz T, Schuchardt JP, Möller K, et al. Low daily dose of 3 mg monacolin K from RYR reduces the concentration of LDL-C in a randomized, placebo-controlled intervention. Nutr Res. 2016;36: 1162–70.

44. Sanidas E, Grassos C. The role of nutraceuticals in the treatment of primary dyslipidemia. Hellenic J Cardiol. 2020;61:60–2.

45. Cicero AFG, Benvenuti C, Moweb AR, et al. Efficacy of a red yeast rice-based nutraceutical in large subgroupsof hypercholesterolemic subjects in every day clinical practice. Mediterr J NutrMetab. 2010;3: 239–46.

46. Solà R, Valls RM, Puzo J, et al. Effects of poly-bioactive compounds on lipid profile and body weight in a moderately hypercholesterolemic population with low cardiovascular disease risk: a multicenter randomized trial. PLoS One. 2014;9: e101978.