Diet and Lipid-Lowering Nutraceuticals in Familial Hypercholesterolemia

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Familial hypercholesterolemia is a genetically determined disease characterized by elevated plasma total and LDL cholesterol levels from the very first years of life, leading to early atherosclerosis. Nutritional intervention is the first-line treatment, complemented with nutraceuticals and drug therapy when necessary.

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1. Introduction

The term “nutraceutical”, coined by DeFelice in 1989, originates from the fusion of “nutrition” and “pharmaceutical”. It refers to a food or a component of food that can exert a positive impact on human health, comprising preventive and therapeutic actions for a specific disease. Nutraceuticals mildly lower the lipid plasma levels, and their safety and tolerability profile in adulthood are universally proven. The action of nutraceuticals on lipid metabolism involves various pathways modulating the inhibition of cholesterol absorption, synthesis, and metabolism; this multifaceted approach can be complemented with dietary and lifestyle intervention, other nutritional compounds, and drug treatments [1]. Nutritional compounds favor several pleiotropic outcomes: they improve the activity of the endothelium and the characteristics of arterial vessels’ walls while counteracting inflammation and oxidative processes [2]. Additionally, patients who do not tolerate statin therapy often find nutraceuticals to be a more acceptable alternative [3]. Subjects aged over 75 years and subjects who, despite being treated with statins or ezetimibe, have LDL cholesterol values off target, may achieve a better lipid profile by combining drug therapy with nutraceuticals [4]. In fact, the European Atherosclerosis Society indicates [5] nutraceuticals as compounds that can be used to lower cholesterol plasma values in well-defined groups of patients with hypercholesterolemia (subjects older than 18 years of age and pediatric patients aged more than six years). The effects of nutraceuticals in pediatric patients with dyslipidemia have been analyzed in some randomized controlled protocols, most times involving small population samples. The main studies on the use of nutritional compounds in pediatric patients focus on fibers and phytosterols/stanols. In contrast, studies regarding red yeast, soy proteins, probiotics, omega-3 fatty acids, and nuts are occasional and not aggregate [6]. In the 2021 European Society of Cardiology (ESC) Guidelines on cardiovascular disease prevention in clinical practice [7], nutraceuticals are described as potentially useful in dyslipidemia treatment, yet the lack of evidence-based studies for most nutraceuticals is highlighted. Moreover, a warning is issued regarding the absence of studies stating that nutritional compounds may exert a preventive action against CHD-related morbidity and mortality [6]. Lipid nanoparticles are bioactive carrier systems

that can improve transport, pharmacokinetics, and stability of encapsulated nutraceuticals; nanoemulsions and microemulsions have also been employed [8]. These formulations have been utilized to deliver nutraceuticals for the treatment of hypercholesterolemia in adult subjects, such as polyphenols and bergamot [9]. Some, but not all, guidelines for dyslipidemia include nutraceuticals among potentially effective treatment options for mild dyslipidemia. It should always be remembered, however, that the evidence regarding the beneficial effects of nutraceuticals on certain endpoints, such as heart stroke and CHD-related diseases, is often poor.

As for their action on cholesterol metabolism, nutraceuticals that can lower plasma lipid values may be subdivided into three main categories: inhibitors of intestinal cholesterol absorption, inhibitors of liver cholesterol synthesis, and inducers of cholesterol excretion. Nevertheless, they often act through multiple and sometimes unclear pathways, yet providing an overall protective effect on lipid metabolism and atherosclerotic process rate decrease [1][2].

2. Nutraceutical Inhibitors of Intestinal Cholesterol Absorption

Fibers are components of plant foods formed by carbohydrates that resist digestion in the gastrointestinal tract. Viscosity is the mechanism through which fibers exert their lipid-lowering effect: Viscous water-soluble fibers act as a gel and bind to bile salts in the intestine, increasing their elimination through feces. Bile is mainly synthesized by cholesterol; thus, when bile salts are excreted at a higher rate, a greater quantity of cholesterol may be available for liver bile synthesis. The higher the fiber's viscosity, the more extensive their cholesterol-lowering effect [10]. Moreover, short-chain fatty acids (SCFA), produced through gut fiber fermentation, may play a protective role in terms of lipid profile modification [11]. The positive impact of fiber on fat-related metabolic pathways has been proven, as fiber helps to reduce both the total and LDL cholesterol levels in the plasma [12], and this has also been acknowledged by the European Food Safety Authority (EFSA) [13]. The effect of fiber intake on lipid plasma values has been analyzed in various studies [14][15]. Nutritional supplementation with oat β-glucan [16][17], psyllium [18][19], pectin, guar gum, and glucomannan [20] significantly reduces the LDL cholesterol plasma values [21]. The majority of trials investigating the lipid-lowering effects of fibers in pediatric subjects highlighted a satisfying adherence to the given treatment, which may be attributed to the pleasant taste of nutraceuticals. The side effects of diarrhea and abdominal pain were only sporadically reported [6][21]. However, the prolonged supplementation of fibers in children and adolescents cannot yet be considered entirely safe, as data on this topic are still limited.

Phytosterols and stanols are bioactive components derived from plants, sharing a structural resemblance to cholesterol. Phytosterols are steroid alkaloids similar to cholesterol, except for their lateral chain. In contrast, stanols are 5α-saturated derivatives of plant sterols. Since phytosterols and stanols cannot be synthesized by humans, their dietary intake through food is crucial. Foods rich in these compounds include fresh fruits, nuts, vegetables, seeds, cereals, pulses, and vegetable oils [22]. The evidence regarding the effect of phytosterols in pediatric subjects is still limited, but recent trials have demonstrated that supplementation with plant sterols is associated with a decrease in the total cholesterol plasma values in pediatric subjects with moderate hypercholesterolemia [23] and in those with familial hypercholesterolemia [24]. Supplementing pediatric subjects with

familial hypercholesterolemia following the CHILD I or CHILD II dietary treatment [25] with 1.2–2 g/day of plant sterols resulted in an over 10% decrease in plasma LDL cholesterol values. Furthermore, increasing the daily intake of phytosterols to 2.3 g led to an even greater reduction in LDL cholesterol plasma values [24]. Plant sterols and stanols typically exhibit a good safety profile, with reported adverse effects being minor up to now. However, available evidence in this context is still limited, and further studies on longer supplementation periods are necessary [6]. Plant sterols and stanols should be considered as valuable therapeutic options in pediatric patients with hypercholesterolemia. It is important to bear in mind that nutritional and lifestyle counseling, and when necessary, pharmacologic therapy, are the cornerstones of treatment during the developmental age [26].

Probiotics are defined as “vital microorganisms that, when consumed in sufficient quantity, confer health benefits to the host”. Recently, a few studies have reported a positive outcome of probiotics on lipid profiles. However, the trials conducted so far lack homogeneity in terms of their duration, the strains of probiotics, dosage, study population, and the types of carriers [27]. Probiotics influence lipid metabolism, but the molecular mechanisms involved are still not clear and well defined. One hypothesis is that probiotics can bind to cholesterol in the intestine or incorporate it into their cell membrane. Lactobacillus acidophilus and Lactobacillus bulgaricus possess enzymes capable of catalyzing cholesterol modifications, thus exerting a favorable action on cholesterol elimination through feces [27]. Other probiotics can reduce the gut–liver flow of bile salts by activating bile salt hydrolase. Some strains of Lactobacilli and Bifidobacteria act by deconjugating bile acids through an enzyme-like mechanism, enhancing their elimination and promoting the systemic hepatic mobilization of cholesterol for the de novo synthesis of bile salts [28]. Certain probiotics may also influence the gut pH, micelle formation, and the transport of lipoproteins, cholesterol, and cholesterol esters [27]. The mechanisms by which probiotics act on lipid metabolism are currently theoretical, and further evidence is needed to determine the extent of their effect on the plasma lipid levels. Importantly, probiotics can be used safely, with no significant reported side effects [6].

3. Nutraceutical Inhibitors of Liver Cholesterol Synthesis

Red yeast rice (RYR) and policosanols are nutraceuticals whose principal mechanism of action is the inhibition of hepatic cholesterol synthesis.

Certain specific yeasts (*Monascus purpureus*, *M. pilosus*, *M. floridanus*, *M. ruber*) in rice (*Oryza sativa*) can produce RYR through fermentation processes. RYR has a long history of use in China, where it has been employed for centuries to enhance the taste of food [29]. Monacoline K, derived from red rice fermented by *Monascus purpureus*, inhibits the activity of 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMGCoA) reductase in the liver, consequently reducing endogenous cholesterol synthesis. The structure and function of Monacolin K are similar to those of lovastatin [30]. The lipid-lowering effect of RYR is dependent not only on Monacolin K but also on many different kinds of monacolin and other compounds such as phytosterols, fibers, and niacin, which can also have a positive effect on lipid metabolism [29][30]. In line with the EFSA’s guidance in 2011, RYR which contains Monacolin K ≤ 10 mg/die can be used in adult subjects provided that their CHD risk is mild or moderate and that their LDL cholesterol plasma values do not exceed 25% of the therapeutic goals, despite nutritional and lifestyle treatments [31][32]. However, in the last decade, potential safety concerns related to the use of nutraceuticals and/or

foods containing RYR-derived Monacolin have been raised. In June 2022, the Commission Regulation of the EU declared that each nutraceutical portion for daily consumption should contain no more than 3 mg of RYR-derived monacolins. Consequently, nutraceuticals with a daily dose of RYR-derived monacolins higher than or equal to 3 mg/day will be banned in Europe, and mandatory mentions and warnings must be present on the labeling of nutraceuticals with RYR-derived monacolins [33]. RYR has not been extensively studied in children and adolescents. Since Monacolin is similar to lovastatin, individuals younger than 18 years of age receiving RYR should be closely monitored, both biochemically and clinically. It is crucial to ensure that RYR is pure and contaminant free [34]. In conclusion, RYR may be considered for the treatment of pediatric patients with hypercholesterolemia, but those undergoing treatment with RYR must remain under continuous medical supervision and undergo regular biochemical and clinical follow-ups [35].

Policosanols (PCSs) are a combination of long-chain alcohols derived from plant waxes, sugar cane, rice bran, and potatoes [36]. In recent years, PCSs have been extensively used as a treatment for dyslipidemia in Cuba [37]. Available evidence on PCSs' use in pediatric patients with dyslipidemia is still scarce [35], without clear evidence of their efficacy and safety. At present, PCSs are not recommended in subjects younger than 18 years old [38][39].

4. Nutraceutical Inducers of LDL Cholesterol Excretion

Some nutraceuticals can promote an increase in LDL cholesterol excretion, thus enhancing LDL receptor expression and prolonging its half-life on the hepatocyte surface. The ultimate result of these processes is the lowering of plasma lipid values. Soy and lupins are the most studied foods exerting this action.

Soy is a bean (Glycine max) which is derived from an Asian plant and it has several notable dietary characteristics. It contains a high percentage of proteins (36–46%), essential amino acids, lipids (18%), soluble carbohydrates (15%), and fibers (15%). Additionally, soy includes important micronutrients such as soy lecithin (0.5%), sterols (0.5%), and tocopherols (0.02%). Soy has been extensively studied for years for its nutritional properties and significant positive health effects, and epidemiologic data suggest the existence of an inverse relationship between soy intake and CHD [40]. In a recent trial, the impact of soy intake on lipid plasma values was investigated in a population of children with familial hypercholesterolemia who were administered soy for 13 weeks. In the intervention group, the LDL cholesterol plasma values were 10% lower after treatment compared to the pre-treatment levels [41]. However, it is worth noting that if soy intake is elevated and prolonged, its isoflavones content could potentially interfere with thyroid function and fertility. In addition, soy has a high content of phytic acid, which may reduce the absorption of calcium, magnesium, copper, iron, and zinc.

Lupins are legumes with a composition poor in salt and with a low glycemic index, and no phytoestrogens. Lupins' macronutrients are distributed as follows: proteins (30–35%), fibers (30%), carbohydrates (3–10%), and lipids (6%), with 81% of the lipids being polyunsaturated fatty acids. Lupin use is generally considered safe, and they have only minor and transient adverse effects [42]. However, lupins can lower plasma lipid values based on the consumed dose, which may impact therapy adherence for extended periods [4].

5. Nutraceuticals with Mixed Action

This category of nutritional compounds includes nutraceuticals with multiple actions, often not totally understood. Polyunsaturated long-chain fatty acids (Lc-PUFAs) are the most analyzed compounds in this category.

Omega-3 Lc-PUFAs can be naturally found in both animals (for example, fish, krill, eggs, squid), and vegetables (for example, seaweeds, nuts, flax seeds, and sage). Protection against cardiovascular disease, as assessed by trials on epidemiology and intervention, have been widely recognized. Recently, the EFSA [43], the American Heart Association (AHA) [44], and the Food Standard of Australia and New Zealand (FSANZ) [45] have endorsed omega-3 LCPUFAs as effective nutraceuticals for CHD. The EFSA states that a 2 g/day intake of docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) can help keep plasma triglycerides values within the normal range, whereas the AHA suggests 2–4 g/day DHA and EPA supplementation to reduce triglyceride plasma values by 25–30% [44]. There is limited evidence on the effects of LCPUFAs on lipid profiles in children and adolescents. The European Society for Paediatric Gastroenterology Hepatology and Nutrition (ESPGHAN) has studied their overall healthy effect in pediatric subjects [46], whereas LCPUFAs' action on lipoproteins in children with dyslipidemia has been described by Engler et al. in the "Effect of Docosahexaenoic Acid on Lipoprotein Subclasses in Hyperlipidemic Children" (EARLY) study [47]. Lc-PUFAs have few adverse effects and their use is considered safe, but they are not always very palatable because they are derived from fish. Seaweed-derived omega-3 Lc-PUFAs should be considered to improve patients' compliance with therapy.

The mechanisms of action and main characteristics of the analyzed nutraceuticals are summarized in **Table 1**.

Table 1. Mechanisms of action and main characteristics of nutraceuticals.

Mechanism of Action	Nutraceutical	Main Characteristics
Inhibition of intestinal cholesterol absorption	Fibers	Increase in fecal cholesterol excretion; Inhibition of hepatic cholesterol synthesis.
	Phytosterols and stanols	Decrease in intestinal absorption of exogenous cholesterol; Competition with cholesterol in the formation of solubilized micelles.
	Probiotics	Increase in fecal cholesterol excretion; Inhibition of the formation of solubilized micelles.
Inhibition of liver cholesterol synthesis	Red yeast rice	Inhibition of HMG-CoA reductase, key enzyme in endogenous cholesterol synthesis.
	Policosanols	Reduction in the cellular expression of HMG-CoA reductase, resulting in reduced cholesterol synthesis.
Induction of LDL cholesterol excretion	Soy and lupin proteins	Down-regulation of expression of SREBP-1, with decreased hepatic lipoprotein secretion and cholesterol content;

Mechanism of Action	Nutraceutical	Main Characteristics
		Regulation of SREBP-2, with increased clearance of cholesterol from the blood.
Mixed actions	ω-3 polyunsaturated long-chain fatty acids	Reduced synthesis of hepatic Very-Low-Density Lipoprotein (VLDL); Reduction in available substrate for the synthesis of new triglycerides; Reduction in the activity of triglyceride-synthesizing enzymes.

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