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THE ROLE OF NUTRACEUTICALS IN THE MANAGEMENT OF DYSLIPIDEMIA AND THEIR EFFECTS ON LIPID METABOLISM: A SYSTEMATIC REVIEW

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ABSTRACT

Dyslipidemia is one of the top modifiable causes of ASCVD, which is still the leading cause of death worldwide. Statins are first line treatment, but potentially reversible obstacles to effective treatment include patient discontinuation, statin intolerance, concern about statin-related adverse effects, and residual cardiometabolic risk in patients who are apparently well treated with statins. Over the years, nutraceuticals have also been of interest as adjunctive agents affecting lipids, but also glucose metabolism, inflammation, intestinal absorption of cholesterol, and vascular biology. Today, their role is not to replace established pharmacological therapy but to complement it in selected patients with low or moderate cardiovascular risk, or patients who are statin-intolerant or statin-ineligible (Penson & Banach, 2020; Cicero et al., 2017; Banach et al., 2018). Here we review the clinical and mechanistic evidence for selected nutraceuticals used for dyslipidemia and other components of the metabolic syndrome. These include red yeast rice, soluble
fiber, omega-3 fatty acids, phytosterols, berberine, bergamot polyphenols, curcumin, and other common functional foods. We also describe issues related to the quality of preparation, inter-individual variability in pharmacokinetics and -dynamics, bioavailability, untoward side effects, and the relationship of surrogate marker changes to hard cardiovascular outcomes. An additional aspect sometimes discussed includes the therapeutic dilemma of statin intolerance and the nocebo effect in the clinical setting (Banach et al, 2015; Banach et al., 2018; Mach et al., 2020). In general, there is support for the use of several nutraceuticals in the primary prevention setting, in partially statin intolerant patients and on top of standard therapies. Even though the effect sizes are not dramatic, they can be clinically meaningful in defined patient populations. On the other hand, this field is still marred by a lack of product standardization, poor quality of studies, and a lack of large outcome-driven clinical trials. Nutraceuticals should be seen as one component of a thorough prevention strategy and not a replacement for evidence-based pharmacotherapy. Nutraceuticals used to lower dyslipidemia are red yeast rice, soluble fiber, omega-3 fatty acids, phytosterols, and berberine.

Objective: To evaluate the role of nutraceuticals in the management of dyslipidemia and to assess their effects on lipid metabolism based on currently available clinical evidence.

Materials and methods: A thorough review of published peer-reviewed studies on the pharmacological role of nutraceuticals in the treatment of dyslipidemia and in the modulation of lipid metabolism was conducted, which included meta-analyzes, systematic reviews, randomized controlled trials, placebo-controlled clinical studies, expert position papers and international guidelines to evaluate their efficacy, safety, and application in dyslipidemic patients.

We focused on the nutraceuticals with lipid-lowering effects, specifically omega-3 fatty acids, red yeast rice, plant sterols and stanols, soluble fiber, berberine, bergamot, cocoa
products, curcumin, coenzyme Q10, and nutraceutical combinations. The inclusion criteria were studies that addressed the management of dyslipidemia with lipid-specific endpoints, of which total cholesterol, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and triglycerides were the most relevant ones. Evidence regarding the putative mechanisms of action of nutraceuticals on lipid metabolism, as well as the effect of nutraceuticals as an add-on or alternative lipid-lowering therapy, was particularly highlighted. Results were narratively synthesized based on the type of nutraceutical and the reported effect on lipid profile and cardiometabolic risk outcomes

KEYWORDS

Dyslipidemia, Nutraceutics, Lipid Metabolism, CVD, Cholesterol

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1. Introduction

Dyslipidemia plays a dominant role in atherosclerotic cardiovascular disease, with heightened low-density lipoprotein cholesterol, triglyceride-rich lipoproteins, and other alterations in lipoprotein metabolism promoting plaque formation and vascular injury. These lipid abnormalities are seldom isolated but part of a wider cardiometabolic syndrome which includes insulin resistance, visceral obesity, chronic low-grade inflammation, impairments of endothelial function and dysbiosis. In this sense, dyslipidemia should be seen as one component of a systemic cardiometabolic syndrome rather than a specific laboratory abnormality and indicated as one hallmark of the cardiovascular disease and the whole vascular tree. Despite the explosion of pharmacological treatments with statins, ezetimibe and PCSK9-targeted therapies, LDL-C goals are often not achieved. The causes are complex and multifactorial, including, but not always attributable to, true intolerance, including muscle-related complaints. Others stop treatment or medication due to fear, confusion, or non-medical information. These reactions may be ascribed to the pharmacological effects of the drug, but in most cases, they appear to be better explained by expectation, prior beliefs, or framing the medication as dangerous or ineffective. The nocebo or 'drucebo' effect has also been investigated in this context (Banach et al. , 2015; Banach et al. , 2018). Nutraceuticals may help close the divide between what can be achieved in the tightly controlled clinical environment and what can be maintained in the usual clinical practice. The word 'nutraceutical' is a portmanteau term of nutrition and pharmaceutical, and is used to describe bioactive nutrients from food also used as pills, powders, and other concentrates. Nutraceuticals are considered to be a middle ground between dietary intervention and prescription medication. That intermediate position is one reason they are appealing to patients who may resist standard drug therapy, and an important reason they are worthy of serious clinical attention, rather than casual enthusiasm (Penson & Banach, 2020; Cicero et al. , 2017). The appeal of nutraceuticals includes biologically plausible mechanisms of action, reproducible lipid-altering effects, and generally good tolerability. Some of these drugs, most notably those directly targeting cholesterol biosynthesis, can be expected to have less potency than high-dose statin therapy; others, which reduce absorption or act on hepatic receptors or through anti-inflammatory effects, may not be directly comparable. In low risk patients, patients with partial statin intolerance, or as an adjunct to lifestyle modification, a modest and persistent lipid-modifying agent may be helpful (Banach et al. , 2018; Mach et al. , 2020). The aim of this review was to summarize and critically appraise the clinical evidence about nutraceuticals in dyslipidemia and cardiometabolic primary prevention. It does not aim to establish nutraceuticals as equivalent in efficacy but rather to categorize nutraceuticals according to the strength of the data supporting their use. This classification includes nutraceuticals with solid scientific evidence, nutraceuticals with preliminary evidence but that are not yet established, and nutraceuticals that have become popular despite insufficient evidence to recommend them.

2. Evidence Base and Scope of the Review

Review articles describing the effects of different nutraceuticals are very heterogeneous, and sometimes even difficult to interpret due to differences in populations, doses and formulations. Therefore, reviews which are able to combine mechanistic data and clinical data, and do not attempt to combine the biology and practice of nutraceuticals, are the most useful. That is the approach taken here. The review therefore focuses on nutraceuticals that have at least a meaningful human evidence base, such as randomized controlled trials, meta-analyzes and systematic reviews. Additionally, red yeast rice, soluble fiber, omega-3 fatty acids, phytosterols, berberine, bergamot polyphenols and curcumin will also be included, as functional foods are often situated at the intersection of dietary and nutraceutical approaches and this intersection is not necessarily well defined in the real-life clinical practice setting (Arisi et al. , 2024; Ojo et al. , 2021; Barkas et al, 2020). I have deliberately not attempted to write a narrow, technical review of one metabolic pathway, because dyslipidemia is far too clinically important. Instead, the discussion is based on the clinical questions that clinicians and patients actually ask: How strong is the effect? How reliable is it? What is the mechanism? Who is most likely to benefit? Not least among these considerations is the question of whether the change in lipid marker represents anything meaningful at all.

3. Red Yeast Rice and Monacolin K

Red yeast rice, the most pharmacological nutraceutical of the lipid lowering nutraceuticals, contains the active ingredient monacolin K, which has the chemical structure of lovastatin. Consequently, red yeast rice lowers cholesterol in the same manner as statins through the competitive inhibition of HMG-CoA reductase, hepatic cholesterol synthesis, and compensatory upregulation of LDL receptor expression in the vasculature of liver cells (hepatocytes), which increases the clearance of LDL cholesterol from circulation (Heinz et al. , 2016; Trogkanis et al. , 2024).

The clinical effect is well established, with red yeast rice lowering LDL-C by 15% to 25% in randomized controlled trials and meta-analyzes. Some red yeast rice products have effects similar to low-dose statin drugs (Heinz et al. , 2016, Trogkanis et al. , 2024). This makes red yeast rice a relatively strong nutraceutical treatment for lowering lipid levels. This probably explains why some patients unwilling to take a prescribed statin will take red yeast rice. It is still called "natural", despite the mechanism of action being readily known pharmacologically.

But this difference is important because the term "natural" can sometimes be a false assurance. Red yeast rice is not just a food supplement. Overall, it is an active product and its effects depend on dosage, stability of the active ingredients, quality of the product, and the susceptibility of the host. The issue of differing amounts of monacolin K in dietary supplements produced from different sources is a major practical drawback of lovastatin, since two dietary supplements with the same name may produce different clinical effects. This issue is highlighted in systematic reviews and expert opinion on lipid-lowering nutraceuticals (Trogkanis et al. 2024; Cicero et al. 2017).

Safety should also be a concern; since monacolin K is a statin-like molecule, it may have the same side effects as statins, including myopathy and drug-drug interactions, particularly those involving the enzyme CYP3A4. In addition, another potential problem is that the process used to produce red yeast rice may also produce citrinin, which is a nephrotoxic and teratogenic mycotoxin. The bottom line is that red yeast rice is not a panacea. Red yeast rice is a nutraceutical with real pharmacology, and care and caution need to be exercised in its use, because that pharmacology needs to be respected (Trogkanis et al. , 2024).

Practically speaking, red yeast rice may be therapeutically useful for patients with mild to moderate hypercholesterolemia who are statin hesitant or selectively statin intolerant, and would be expected to accept only a portion of HMG-CoA reductase inhibition. In practice, red yeast rice may not be appropriate for patients who require more powerful risk reduction and/or more predictable reduction in LDL. In this setting, standard lipid-lowering therapy (LLT) is the better choice (Banach et al. , 2018; Penson & Banach, 2020).

4. Soluble Fiber as a Reliable Lipid-Lowering Intervention

If red yeast rice is the nutraceutical closest to a drug, soluble fiber is the most physiologically intuitive nutraceutical and has the most reproducible effect. Psyllium, beta-glucans, pectins and related fibers improve lipid metabolism in the gut by increasing the viscosity of intestinal contents, binding bile acids, decreasing cholesterol reabsorption and increasing the need for circulating cholesterol to be metabolized into bile acids. This results in a small but consistent lowering of LDL-C and, to a lesser extent, total cholesterol levels (Ghavami et al. , 2023).

The most valuable aspect of soluble fiber is the dose-response relationship: the more fiber consumed, the greater the reduction of lipids (though not to an unlimited extent). Though the effect may be small, it is of such reliability that it may be more clinically useful than a more marked effect that depends upon a product of variable concentration or work that may be poorly tolerated.

In addition to lipid lowering, soluble fiber reduces postprandial glycemia, slows glucose absorption, increases satiation, and improves the gut microbiota. In patients with type 2 diabetes or metabolic syndrome, these effects of soluble fiber are not peripheral to treatment, as its fermentation in the colon produces short-chain fatty acids, which may be in part responsible for the metabolic homeostatic and anti-inflammatory signaling benefits. These changes in gut microflora may also be associated with a reduction in endotoxemia and inflammatory markers including high-sensitivity CRP (Ojo et al. , 2021).

The variety of metabolic effects indicates that soluble fiber should be in a central position in terms of nutraceutical prevention because it is relatively inexpensive, widely available, probably safe, and probably

easier to apply to daily practice than other nutraceuticals. The main limitation is adherence; like any dietary intervention, it can only work if people follow it. However, this is a practical, rather than conceptual, problem; the biology of the concept is sound (Ghavami et al. , 2023; Ojo et al. , 2021).

5. Omega-3 Fatty Acids: Marine LCn3 versus ALA

Different omega-3 fatty acids are often grouped together as one, while marine long-chain omega-3 fatty acids (mostly EPA and DHA) are not the same as plant omega-3 ALA. Omega-3 prescription medication is not the same as over-the-counter fish oil products.

These differences are important as the lipid effects, clinical outcomes, and populations most likely to benefit differ (Abdelhamid et al. , 2018; Sala-Vila et al. , 2022).

EPA and DHA are the most studied CVD nutraceuticals, with the most consistent effect being a reduction in triglycerides due to decreased hepatic production of triglycerides, decreased production of very-LDL, and increased clearance of the triglyceride-rich particles. This makes them especially useful in people with hypertriglyceridemia or mixed dyslipidemia, where triglyceride lowering can be clinically meaningful, especially at high baseline triglyceride levels (Abdelhamid et al. , 2018).

The harder question is whether this biochemical improvement translates into fewer cardiovascular events. The answer is more complicated. Review papers have suggested that the increased consumption of omega-3 fatty acids has little to no effect on all-cause mortality or major cardiovascular events for most groups (Abdelhamid et al. , 2018). The biologically plausible effect size is not explained by a lack of biological plausibility, but rather, depends on several factors. The most consistently positive results have been reported with purified EPA at high doses among high risk patients, suggesting that the effect of omega-3 fatty acids could be specific to the dose, compound and indication rather than the class (Sala-Vila et al. , 2022).

Alpha-linolenic acid (ALA) is also a major constituent of flaxseed, walnuts and some vegetable oils. It is a precursor to long-chain omega-3 fatty acids, but humans can only convert a small amount. ALA appears to have modest cardioprotective effects and may also have some antiarrhythmic effects. Its cholesterol-lowering effects are weaker than those of marine LCn3 and an inverse association between ALA intake and coronary risk is suggested by some epidemiological data, but the magnitude of this benefit is much smaller than many people assume (Sala-Vila et al. , 2022). While ALA is safe in the usual amount in food as part of a healthy diet, it is not a replacement for prescription amounts of EPA.

The take-home lesson of omega-3 research is that form matters. Dose matters. Population matters: saying that "omega-3s reduce cardiovascular risk" is too broad to be clinically useful: it is the details that will determine the outcome (Abdelhamid et al. , 2018; Sala-Vila et al. , 2022).

6. Phytosterols and the Biology of Intestinal Cholesterol Handling

Sterols such as beta-sitosterol and campesterol are similar in structure to cholesterol and act to reduce absorption of cholesterol by competing to be incorporated into micelles. This mechanistic pathway is relatively well supported. The standard dose of 2 g/day lowers LDL-C by 5% to 10% and can be a reasonable alternative for those with mild hypercholesterolemia or for those who prefer a dietary approach (Fumeron et al. , 2017). Their effects are often described in percentage or relative terms rather than in absolute terms. This matters. Due to the denominator difference, a person with a higher starting LDL-C may experience a greater absolute reduction than someone with lower starting LDL-C. Phytosterols are best used as first line therapy when cholesterol is moderately elevated, and when drug therapy is not called for, having a greater potential to impact higher LDL-C.

The most interesting feature, however, is the variability in phytosterol response, as not everyone responds identically and a meaningful number of people seem to be non-responders. Among genetic factors, the genotype for apolipoprotein E is associated with the response, as E4 carriers absorb more dietary cholesterol and make less cholesterol, making them potentially more responsive to dietary changes. The opposite is true for E2 which already absorbs poorly, so one may see less of a reaction. This is a tautological reminder, that is, nutraceutical responses are not random, and absorption is often polymorphic. It is biologically patterned (Fumeron et al. , 2017).

Additional genes including sterol transporters ABCG5 and ABCG8 may participate in baseline lipid metabolism but do not strongly predict response. CETP variation may predict response but appears to be less common. Some studies suggest certain CETP genotypes may be associated with worse response or increase LDL in response to phytosterol treatment. It may still be debated whether such observations should lead to real clinical practice involving genotype-guided drug administration. However, the underlying principle is that response heterogeneity is real and should not be ignored (Fumeron et al. , 2017).

For childhood familial hypercholesterolaemia, phytosterols and stanols may only have a short-term dietary role, and are not a replacement for future pharmacotherapy, but are important as they might reduce the lifetime LDL-C exposure by moderately lowering LDL-C concentrations during a critical 10-year period preceding the application of more intensive therapy. That is clinically meaningful even when the short-term effect appears to be small (Barkas et al. , 2020).

7. Berberine as a Multi-Target Metabolic Compound

Berberine is one of the most important nutraceuticals in the lipid field, but it cannot be defined with a specific mechanism of action, because it is not a statin, a pure absorption inhibitor, or a simple anti-inflammatory agent. Rather, it affects several metabolic pathways at the same time.

One well-described effect is upregulation of LDL receptor expression (through stabilization of LDLR mRNA), leading to increased hepatic LDL-C clearance. Inhibition of PCSK9 (an enzyme that degrades LDL receptors) is another proposed mechanism of action of berberine. Berberine may increase clearance of LDL by inhibiting PCSK9, thus increasing the number of LDL receptors, and activating AMPK (AMP-activated protein kinase), an energy sensor that plays a central role in regulating glucose metabolism, lipid oxidation and insulin sensitivity (Penson & Banach, 2020; Cicero et al. , 2017).

The clinical result is a compound able to lower LDL-C and triglycerides, and improve glycemia, of interest for patients with metabolic syndrome or mixed dyslipidemia, with insulin resistance. It is also one of the few nutraceuticals with the potential to improve multiple metabolic abnormalities simultaneously.

In contrast, berberine is poorly absorbed, which may explain some of the heterogeneity in the effect. Furthermore, many studies into the CAER effects are small and restricted to particular geographic areas, limiting the applicability of results. This does not invalidate the results, but does point to the necessity of caution in interpreting the finding. A compound can also have biological plausibility but be unable to be used in a clinical setting (Kłosiewicz-Latoszek et al. , 2021; Penson & Banach, 2020).

The question for providers is therefore not whether berberine works, but rather whether it works well enough, in the right formulation and in the right patient population, to warrant its use in clinical practice. The answer appears to be yes in certain patients, although not as a substitute for established lipid lowering therapy.

8. Bergamot Polyphenols and the Role of Citrus Flavonoids

Bergamot extracts have received attention due to the presence of a particular mix of flavonoids (neoeriocitrin, naringin and neohesperidin), which could have a statin-like effect on cholesterol metabolism, albeit through different and less understood mechanisms. Clinical trials have shown reductions in LDL-C and triglycerides with the use of bergamot supplement. In other studies, the effect size has been relatively large, with substantial between-study heterogeneity, likely due to the varying extract formulations, doses, treatment duration, and study designs (Kłosiewicz-Latoszek et al, 2021).

The potential effects of bergamot via inhibition of multiple pathways of lipid biosynthesis, intestinal absorption and inflammation, make it an attractive nutraceutical agent for patients with mild hypercholesterolemia, mixed dyslipidemia, and for patients with statin intolerance. It may also be a useful alternative for patients with a dislike to synthetic medications.

However, the evidence is less reliable than evidence for soluble fiber or red yeast rice, and trial sizes are often small. Results for different products cannot be reliably compared because they are not chemically identical. This is a common issue in nutraceutical research, as promising effects are often reported before the field has standardized the compound enough to make confident comparisons. Bergamot is no exception. While interesting and potentially useful, more research is needed before it can be given a consistent guideline positioning at a level that would be considered routine (Kłosiewicz-Latoszek et al. , 2021; Cicero et al. , 2017).

9. Curcumin and the Intersection of Lipid Biology and Inflammation

Discussions of curcumin in dyslipidemia focus less on its anti-inflammatory and antioxidant properties, and more on the fact that atherosclerosis is not just a lipid storage disorder, but an arterial wall inflammatory disease. From this point of view, compounds that attenuate inflammatory signaling may stabilize plaques or improve the environment in which the dyslipidemia acts.

Curcumin supplementation may help improve lipid profile in patients with metabolic syndrome, as several clinical trials found a reduction in total cholesterol, LDL-C and triglycerides (especially when used with coenzyme Q10, Sangouni et al. , 2022). The main drawback of curcumin supplementation is bioavailability. That said, curcumin is poorly absorbed, and bioavailability can be considerably influenced by the composition of the preparation, meaning that the mode of delivery for a given compound cannot be ignored. Mechanistically, curcumin may affect pathways involved in the regulation of the processes of fatty acid synthesis, adipocyte lipid accumulation and other vascular disease pathways. These are biologically plausible. However, like most nutraceuticals, there are many products that are not equivalent, and therefore the label does not tell the whole story about the product's efficacy and safety.

Curcumin may be considered for adjunctive use in metabolic syndrome, inflammation associated with obesity, and for patients interested in adjunctive non-pharmacological therapy for dyslipidemia. Curcumin is not indicated for patients with high cardiovascular risk already using lipid lowering medication (Sangouni et al, 2022).

10. Combination Nutraceuticals and the Question of Synergy

Combination nutraceutical therapy is one of the leading approaches. If one compound inhibits cholesterol production, another increases receptor expression, and a third influences absorption or the microbiota, in many cases the resulting change in cholesterol is greater than that induced by any compound acting alone. This appears to be the case in practical application.

The combination of monacolin K plus berberine is especially promising as they modulate different control points of the lipid homeostasis: the former regulates synthesis, the latter modulates the receptor expression and, via PCSK9, the degradation of receptors. In certain patients, other compounds like policosanols and some probiotics may contribute additional lipid-lowering effects. The LDL-C reductions achieved with policosanol-probiotic combination products can be similar to those of low-dose statins, though the actual extent of benefit depends on the formulation used and the study design of the trials assessing them (Protic et al. , 2021; Penson & Banach, 2020).

The problem, as always, is standardization: combination nutraceuticals do not necessarily work better just because they contain more ingredients. In fact, the opposite may be the case, if the ingredients are not individually dosed and/or the product is not standardized across batches, the ability to interpret results in a meaningful way may be compromised. Clinically however, synergy is plausible and for some patients, a poly-pill approach may be the way to achieve a modest and clinically meaningful LDL lowering with acceptable tolerability (Protic et al. , 2021).

This is of particular relevance in statin intolerant patients, unable to tolerate drug treatment, who wish for more than just lifestyle intervention, and this treatment is not intended to displace evidence-based medicine, but only to be a bridge to it (Banach et al. , 2018; Cicero et al. , 2017).

11. Functional Foods and the Border Between Diet and Supplement

Functional foods differ somewhat from concentrated nutraceuticals, but are mentioned in this context because they play an important role in lipid management, and because they are sometimes the scaffolding on which a supplement is built. Cocoa, walnuts, flaxseed, soy protein, garlic, tea and artichoke have all been studied in terms of their effects on lipids or other cardiometabolic markers.

Intake of cocoa flavonoids appears to be associated with a small statistically important reduction in total cholesterol and low-density lipoprotein cholesterol. Cocoa flavonoids may also modestly reduce triglyceride levels, but results are more variable. BMI, and age at baseline may impact results. As with many nutraceuticals, this appears not to be the case for all patients (Arisi et al. , 2024).

Soy protein has mainly been studied in children and adolescents with familial hypercholesterolemia, where dietary modification is most helpful to avoid more intense pharmacotherapy. The effect on lipid levels

of soy protein is sometimes small enough that a study does not reach statistical importance. Soy is best thought of as a cardioprotective diet rather than a lipid drug in itself (Barkas et al. , 2020).

Walnuts and flaxseed have been especially of interest for their alpha-linolenic acid and overall nutritional profiles. High walnut diets have also been associated with reductions in total cholesterol, with reductions in LDL-C and triglycerides in some studies as well. Additionally, total and LDL-C are reduced by flaxseed products, particularly those utilizing the seed as opposed to the flaxseed oil. The form in which the food is consumed may also be important (Sala-Vila et al. , 2022).

Other ingredients mentioned include garlic, tea polyphenols (a diverse group of compounds including catechins) and artichoke extracts. These have a relatively weak cholesterol-lowering effect, but the overall contribution to blood lipids may be small, making a difference through the metabolic milieu. Monacolin K and phytosterols are the most effective. Tea polyphenols may inhibit the incorporation of cholesterol into micelles, thus decreasing cholesterol absorption. Though their effect on serum lipid levels is modest, they appear to be effective (Cicero et al. , 2017).

The strength of functional foods is not in their being substitutes for pharmacotherapy, but in making ways to long-term dietary adherence easier to imagine and maintain. This is not a trivial advantage for many patients.

12. Barriers to Therapy; Uses of Nutraceuticals in Clinical Practice

The greatest challenge in dyslipidemia is not how to lower lipids, but how to best tailor, implement and monitor lipid-lowering therapy to the individual patient with the psychosocial components in mind. Statins are strong lipid-lowering agents, yet patients frequently fail to accept or adhere to statin therapy as a result of concern over side effects or information previously gained from their disease experience. The nocebo effect (also referred to as the drucebo effect in more recent literature) is not a trivial consideration, and indeed can constitute a fundamental obstacle to optimal cardiovascular prevention (Banach et al. , 2015; Banach et al. , 2018).

In that sense nutraceuticals may have a utility above and beyond their potential biochemical benefits: some patients unwilling to take statins may be open to the use of nutraceuticals. This may have the dual utility of bridging them to treatment (as well as potentially overcoming the psychological drug resistance that exists with lipid treatment) and, in some cases, accepting an evidence-based treatment when patients have learned that they are able to tolerate drug treatment with few side effects (Penson & Banach, 2020; Cicero et al. , 2017).

The most important unresolved issues are safety and regulation. Many nutraceuticals are sold as dietary supplements, which means that they may not be manufactured to the same standards as prescription drugs. This is especially problematic when the ingredient is a drug-like compound such as red yeast rice, where the drug-like behavior and quality of ingredients in the formulation cannot be ignored. The same applies to combinations, where the label may misrepresent the composition of the biologically active composition in question (Trogkanis et al. , 2024; Protic et al. , 2021).

This has a clear practical implication and indicates that nutraceuticals are best reserved for selective usage in low or moderate risk patients, those with partial statin intolerance, those who need a modest additional lipid-lowering effect, and those patients who would otherwise refuse treatment altogether, in whom PCSK9 inhibitors may be useful. PCSK9 inhibitors should only be used as an add-on to evidence-based treatment in patients at higher risk (Banach et al. , 2018; Mach et al. , 2020).

13. Conclusions and Future Directions

Nutraceuticals have plausible and justified roles in the management of dyslipidemia and cardiometabolic diseases. Red yeast rice, soluble fiber, omega-3 fatty acids, phytosterols, and berberine have sufficient biological plausibility and clinically meaningful LDL-C lowering with minimal adverse effects (Trogkanis et al. , 2024; Ghavami et al. , 2023; Abdelhamid et al. , 2018; Fumeron et al. , 2017; Penson & Banach, 2020). Other promising options (bergamot polyphenols, curcumin) are still limited by heterogeneity of evidence and formulation issues (Kłosiewicz-Latoszek et al. , 2021; Sangouni et al. , 2022). Functional foods are still an important component of a sustainable dietary approach and should not be discarded due to their less pronounced effects (Arisi et al. , 2024; Ojo et al. , 2021; Sala-Vila et al. , 2022).

The most important conclusion is that nutraceuticals are not panaceas, and should not be viewed as alternatives to statins or other well-studied treatments for high-risk patients. Their effect sizes are typically moderate, and for some of the agents, effects on cardiovascular events are not known, but they can have a role in the right patient, at the right dose, in the right clinical context.

More standardized, better characterized products, larger randomized trials, and studies that use outcomes other than surrogate markers are needed. A greater understanding of genetic, microbiome and other host factors that underlie variation in drug response may allow targeting of patients that are most likely to benefit from the treatment. That is where the field will become more clinically mature. For now, nutraceuticals are best understood as adjunct to prevention efforts that will always be grounded in lifestyle change and evidence-based pharmacotherapy.

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