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REVIEW ARTICLE

Nutraceuticals: Definition and Epidemiological Rationale for Their Use in Clinical Practice

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Abstract Cardiometabolic risk factors, such as hypercholesterolemia, hypertriglyceridemia, metabolic syndrome, diabetes, and arterial hypertension, are major predictors of the premature development of cardiovascular diseases (CVD). Since CVD prevention needs a life-course approach, beyond dietary and pharmacological treatment, non-pharmacological treatment should be considered an important alternative for patients in primary prevention with mild–moderate cardiometabolic risk factors at low-moderate global risk of CVD. Several functional foods and nutraceuticals are efficacious, safe and well tolerated. However, only some (monacolins of red yeast rice and omega-3 fatty acids) have showed, in long-term randomized clinical trials, a reduction of cardiovascular events.

Keywords Cardiometabolic risk factors · Nutraceuticals · Cardiovascular prevention

1 Introduction

Cardiometabolic risk factors, such as hypercholesterolemia, hypertriglyceridemia, metabolic syndrome, diabetes, and arterial hypertension, are major predictors of the premature development of coronary heart disease (CHD) and, in general, cardiovascular diseases (CVD) [1, 2]. Many controlled studies performed with dietary or pharmacological interventions have demonstrated that control of these cardiometabolic risk factors reduced the incidence of major cardiovascular events [3–5]. Since CVD prevention needs a life-course approach, dietary modifications are the first step, being cost-effective in delaying or preventing the onset of CVD. However, in patients with moderate and, above all, with severe levels of risk factors, dietary therapy is often not adequate and drug therapy is required for optimal reduction [6]. Various drugs used to reduce concentrations of cardiometabolic risk factors have exerted significant reductions of the incidence of cardiovascular events in primary and secondary prevention studies [4, 5]. However, drug treatment may be associated with adverse effects and may also be costly. In primary prevention, furthermore, evidence of reduction in total mortality in long-term studies is often missing [7–9]. Therefore, in primary prevention, non-pharmacological treatment could be considered an important alternative for many patients.

2 Non-Pharmacological Treatment of Cardiometabolic Risk Factors

The main indications for non-pharmacological therapy that we could define as the "third road" to prevent CVD are a single cardiometabolic risk factor at mild–moderate levels and a low-moderate global risk of CVD in patients. In addition, we can also consider other specific patients with cardiometabolic risk factors and other characteristics such as: children of parents with premature CVD; premenopausal women; liver and/or renal failure, not yet adequately corrected with available drugs; intolerant to pharmaceutical drugs; consuming multiple drugs; preferring "natural" therapies [10].

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A large number of functional foods or dietary supplements (foods that contains substances that provide medical or health benefits) and nutraceuticals (extracts of foods that provide medical or health benefits) have been studied for their ability to reduce CVD risk factors and to reduce biomarkers of CVD (for example, insulin resistance, systemic inflammation, prothrombotic conditions). Examples are alpha-lipoic acid, berberine, cinnamon, cocoa flavonoids, coenzyme Q10, fibers, garlic, L-arginine, melatonin, minerals such as chromium, potassium and magnesium, monacolins of red yeast rice, olive oil, omega-3 polyunsaturated fatty acids (PUFA), ORTHOSIPHON STAMINEUS, plant sterols, policosanols, polyphenols, soy protein, vitamin C, and vitamin E [10–15].

However, the recent European guidelines of the management of dyslipidemias and a large review cite some functional foods and nutraceuticals as potentially useful lipid-lowering substances: plant sterols, soluble fibers and, respectively, monacolins, and omega-3 PUFA [9, 16]. Also about the natural treatment of hypertension, other large reviews and some trials found that only cocoa flavonoids, coenzyme Q10, garlic, L-arginine, melatonin, ORTHOSIPHON STAMINEUS, omega-3 PUFA, and vitamin C demonstrate evidence of some benefit in the treatment of mild hypertension (and we could also add extra-virgin olive oil) [11, 13, 14, 17]. These agents have been shown to be at least as effective as the incorporation of lifestyle modifications. However, these agents should not replace the implementation of recommended lifestyle changes, including proper diet, exercise, and weight loss, but, on the contrary, the combination of nutraceuticals with dietary counseling reduces cardiometabolic risk factors and calculated Framingham Risk Score [17]. In addition, we have to underline that only monacolins of yeast red rice and omega-3 PUFA have showed, in long-term randomized clinical trials, a reduction of cardiovascular events (morbidity and mortality) [18–20].

Tolerability and safety of functional foods and nutraceuticals is well supported by clinical evidences [10]. However, because these products are easily accessible and because of the frequent misinterpretation that all natural products are also safe, patients may choose these agents directly for cardiometabolic risk factor control. Their self-treatment without the supervision of a medical doctor familiar with their use may be dangerous [10, 11]. For example, patients often utilize with some success garlic in the treatment of mild hypertension. However, garlic is known to interact with some medications: it may enhance the hypoglycemic effects of oral anti-diabetic drugs and the anticoagulant effects of warfarin [11]. Also, omega-3 PUFA have a small increasing effect on anticoagulant drugs during intake of large doses [10]. Acting through a direct inhibition of the 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMGCoA) reductase, monacolins of red yeast extract could potentially have the same side effects as the statins: myopathy and hepatotoxiciy [10]. Moreover, those patients with liver and/or kidney failure and pregnant or lactating women should avoid monacolins, due to lack of safety data. It is also recommended that co-administration with gemfibrozil, cyclosporine, azole-antifungals, erythromycin, clarithromycin, and protease inhibitors be avoided, since monacolins are mostly metabolized by the cytochrome P3A4 [10].

3 Conclusions

Recently, international guidelines on CVD prevention and reviews have recognized that, at least at therapeutic doses, some functional foods and nutraceuticals (such as alpha-lipoic acid, cocoa flavonoids, coenzyme Q10, garlic, L-arginine, melatonin, monacolins, omega-3 PUFA, ORTHOSIPHON STAMINEUS, plant sterols, soluble fibers, and vitamin C) are efficacious (the regulatory agencies could remove them from the list of dietary supplements because of being "too active"), safe and well tolerated in the treatment of cardiometabolic risk factors.

These can be used in primary prevention in patients who are not yet candidates for pharmacological therapy, with the aim of delaying pharmacological treatment, but at the same time treating the risk factors and reducing cardiovascular risk in those patients always at risk, even though not classified as high risk. Data from "Progetto Cuore" ("The Italian Heart Project" of the Italian Institute of Health) demonstrated that men and women with a 10-year cardiovascular risk $\geq$20 % generate only 25 % and, respectively, 4 % of the overall number of yearly cardiovascular events. On the contrary, men and women with a 10-year risk <20 % generate 75 % and, respectively, 96 % of all events [21]. Therefore, in primary prevention, the intervention itargets those patients deemed to be not at high cardiovascular risk and produce a significant reduction in cardiovascular events occurring in the population. Especially some nutraceuticals, namely monacolines of red yeast rice and omega-3 PUFA, have been studied in long-term randomized clinical trials with definitive outcomes (morbidity, mortality). This could also have pharma-economic implications with savings linked not only to patient expense paid without government reimbursement, but also to the reduction of estimated cardiovascular risk [22] and to the reduction of the cost of side effects, usually low with nutraceuticals compared to pharmaceutical drugs. Instead, there are many other dietary supplements and nutraceuticals that are used for their supposed cardiometabolic risk factor-lowering effect, but without adequate scientific support. The clinical trials available in these cases are more

focused on the detection of short-term effects. Instead, a more in-depth understanding of the risks and of pharmacological interactions of the single compounds is needed for the management of frail patients (children, elders, patients with liver or renal failure, patients undergoing multiple drug treatment). Since these products are actually distributed not only in pharmacies, but also in supermarkets and herb shops, information regarding safety and precautions must be communicated compared to chemical drugs, whose use is more strictly monitored by physicians. Therefore, the European Food Safety Agency and the United States Food and Drug Administration, as well as several scientific societies, are working to regulate and monitor their use.

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