REVIEW ARTICLE

The Possible Role of Nutraceuticals in the Prevention of Cardiovascular Disease

Angela Albarosa Rivellese[1] · Paola Ciciola[1] · Giuseppina Costabile[1] · Claudia Vetrani[1] · Marilena Vitale[1]

Abstract

Cardiovascular diseases (CVDs) are the main causes of mortality and disability worldwide. Although the initial therapeutic approach to improve the main cardiovascular (CV) risk factors is based on nonpharmacological measures, mainly lifestyle modifications, compliance to recommendations is often poor and inadequate. Therefore, in recent years the use of several nutraceuticals, i.e., nutrients and/or bioactive compounds of plant or microbial origin with potentially healthful effects, has become widespread. However, to date, the scientific data on the possible benefits of the use of nutraceuticals are still inconclusive, due to the absence of adequately controlled intervention studies at least for some of them. Against this background, the scientific evidence derived from controlled intervention studies in relation to the effects of some nutraceuticals (i.e. fiber, phytosterols, soy products, red yeast rice, polyphenols and berberine) on the main CV risk factors (body weight, blood pressure, blood glucose levels and plasma lipids) in humans will be reviewed.

Keywords Nutraceuticals · Blood glucose · Plasma lipids · Blood pressure · Body weight

1 Introduction

Cardiovascular diseases (CVDs), including coronary heart disease and stroke, are the main causes of mortality and disability both largely preventable through the control of risk factors via lifestyle modifications and preventive medication.

The initial therapeutic approach to the main risk factors for CVDs should always include nonpharmacological measures—such as lifestyle interventions, which are very similar for all CV risk factors [1]. In fact, current recommendations strongly encourage the reduction of total energy intake from foods and the increase in physical activity, especially in overweight/obese individuals. Moreover, saturated fat should be limited to less than 10% of calories, saturated and trans fatty acids should be replaced with polyunsaturated (PUFA) (up to 10% of calories) or monounsaturated (MUFA) fatty acids (10–15% of calories), and dietary fiber

intake should be increased (30–45 g/day). Daily salt intake also should be reduced by at least one third and, if possible, to < 5 g per day. Moreover, dietary patterns that include a variety of fruits, vegetables, seeds and nuts (2–3 servings of each per day), pulses and whole grains are strongly encouraged, to promote health and lower CVD risk [2, 3].

However, adherence to lifestyle modification to prevent CVDs is often poor due to unsatisfactory patient compliance and poor adherence and maintenance in the medium- to long-term [4]. In addition, some dietary components with a potentially beneficial activity on CV risk factors are present only in scanty amounts in food. Therefore, the use of nutraceuticals has become widespread in recent years.

Nutraceuticals are nutrients and/or bioactive compounds of plant or microbial origin, with possible beneficial effects on human health when supplemented in adequate amounts (often above those present in foods). Nutraceuticals may be added to different foods and beverages (as in fortified foods), or taken in the form of dietary supplements (liquid preparations, tablets, capsules).

A growing number of nutraceuticals with variable activity on different CV risk factors have been proposed; unfortunately, scientific research has produced conflicting results for some of them. Hence, the aim of this report is to review and discuss the scientific evidence derived from controlled

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✉ Giuseppina Costabile
giuseppina.costabile@unina.it

[1] Department of Clinical Medicine and Surgery, "Federico II" University of Naples, Via S. Pansini, 5, Naples, Italy

intervention studies regarding the effects of some nutraceuticals (i.e. fiber, phytosterols, soy products, red yeast rice, polyphenols and berberine) on the main CV risk factors (body weight, blood pressure, blood glucose levels and plasma lipids) in humans.

2 Effects on Body Weight

Overweight and obesity are currently recognized as the major risk factors for the development of a number of chronic diseases, including diabetes, dyslipidemia, CVDs and some types of cancer. Due to the dramatic increase in obesity prevalence, researchers have attempted to find effective complementary therapies for obesity and its complications, thus identifying in the supplementation of some nutraceuticals, mainly fibers and polyphenols, a potential tool and strategy to facilitate body weight management and influence obesity associated CV risk factors.

2.1 Fiber

The overall evidence from clinical intervention studies indicates soluble/viscous fibers as the most effective supplements for the management of body weight. Previous meta-analyses of twelve randomized controlled trials (RCTs) evaluated the effects of supplementation of different types of isolated soluble fiber (manno-oligosaccharides, galacto-oligosaccharides, fructo-oligosaccharides, β-glucan, flax-seed mucilage, mannans and dextrin) on outcomes related to weight management. Overall, the results showed that, independently of energy restriction or weight loss counseling, soluble fiber supplementation, compared to placebo, significantly reduced Body Mass Index (BMI) by 0.84 kg/m^2, body weight by 2.52 kg and body fat by 0.41% in overweight and obese adults, at a mean dose of 18.5 g/day, over a follow-up of 2–17 weeks [5]. In line with this trend, findings from a three-arm, parallel, blind RCT on 83 overweight/obese individuals, showed that the supplementation of a commercial soluble viscous non-starch polysaccharide complex (PolyGlycoplex-PGX, as softgels or granules), containing konjac glucomannan, sodium alginate and xanthan gum, for 12 weeks, led to a significant reduction in waist circumference (− 2.5 cm) in the whole study population, as well as a to significant decrease in body weight (− 1.4 kg) in the subgroup of participants who consumed the recommended dose of fiber (about 12.2 g/day) [6].

Isolated glucomannan is also effective in the management of body weight [7, 8]. In fact, results from a glucomannan-focused meta-analysis of 14 RCTs showed a statistically significant, albeit small, reduction in body weight, of 0.79 kg in studies lasting a mean of 5.2 week [7]. However, the benefits observed with glucomannan supplementation on weight loss

were not independent of the dietary modifications implemented in these RCTs. These findings have been confirmed by a meta-analyses of only 6 RCTs, in overweight/obese individuals, reporting a significant effect of glucomannan supplementation on body weight at different points during the intervention periods: at week 2 (− 0.21 kg), week 4 (− 2.04 kg) and week 5 (− 1.3 kg), at an average dose of glucomannan between 1.24 and 3.99 g/day [8].

The positive effect of glucomannan supplementation on the reduction of body weight was already confirmed in 2010 by the European Food Safety Authority (EFSA). The effect claimed is achieved when ≥ 3 g of glucomannan is supplemented daily in three 1-g doses, together with one to two glasses of water before the meal, in the context of an energy-restricted diet.

Other types of soluble fiber supplements, such as psyllium, dextrin and alginate, in combination with an energy restriction program, have proven capable to affect body weight and body composition and thus to be of some help in the management of obesity [9–11].

In conclusion, based on the available evidence in humans, it seems that soluble/viscous fiber supplements may be helpful in the management of body weight; it is nevertheless important to underline that the significant reduction in body weight observed in many studies is of small entity.

2.2 Polyphenols

Among polyphenols, flavonoids appear to be the most involved in obesity and weight management. In particular, epigallocatechin-3-gallate (EGCG), mainly abundant in green tea, represents the subclass of flavonoids best associated with weight loss.

Some years ago, Basu and colleagues [12], in a clinical trial in obese people, showed that an 8-week supplementation of encapsulated green tea extracts, containing 870 mg of catechins, resulted in a statistically significant reduction in body weight and BMI, by 1.9 kg and 0.6 kg/m^2, respectively, compared to placebo. The results of two other randomized controlled trials performed with either encapsulated green tea extracts (800 mg catechins) for 8 weeks or decaffeinated green tea extracts (EGCG 856.8 mg) for 12 weeks confirms the results obtained by Basu [13, 14].

Conversely, other clinical studies have failed to show a beneficial effect of green tea catechin supplements on body weight and/or body composition. There may be different reasons for these discrepancies, one of which may be related to the possible confounding effect of caffeine. In fact, green tea extract naturally contains caffeine, a component known to influence per se body weight and body composition by enhancing sympathetic nervous system activity and regulating appetite [15]. Therefore, as a metabolic stimulant, the concentration of caffeine in green tea extract supplements

should be carefully examined in relation to the independent effects of catechins on body weight. To this regard, a meta-analysis of 15 RCTs tried to characterize the relation between green tea catechins with and without caffeine, with changes in anthropometric parameters in overweight/obese people. This meta-analysis showed that the supplementation of catechins with caffeine, at a dose ranging from 583 to 714 mg/day over a median period of 12 week, decreased body weight, BMI and waist circumference by 1.38 kg, 0.55 kg/m^2 and 1.93 cm, respectively, compared with a caffeine-matched control [16]. On the other hand, the few studies included in this meta-analysis on effects of catechins without concomitant caffeine administration did not show benefits on any of the anthropometric endpoints assessed.

In conclusion, results from RCTs evaluating the effect of tea catechin supplementation on outcomes related to obesity management are still discordant and inconclusive. Several confounding factors can influence the results of the available clinical trials, such as the concomitant presence of caffeine, but also the ethnicity of participants (Asians seems to be more responsive to caffeine) and the implementation or not of weight loss strategies.

2.3 Omega-3 Polyunsaturated Fatty Acids (n-3 PUFAs)

Based on studies performed in animals some years ago, it has been hypothesized that n-3 PUFA supplementation could influence body weight regulation to some extent, by increasing body fat oxidation or energy expenditure [17]. Instead, the evidence from RCTs in humans is limited and very inconsistent. Findings from a meta-analysis of 11 RCTs in overweight/obese adults, showed that n-3 PUFA supplementation, at a mean range dose of 1.5–6.0 g/day for 3 to 24 weeks, has no effects on body weight and/or BMI, compared to placebo. However, a subgroup analyses of only 7 studies included in this meta-analysis, revealed a significant reduction in waist circumference after n-3 PUFA supplementation compared to placebo [18]. In line with these findings, more recently Jacobo-Cejudo and colleagues [19], in a randomized, single-blind, placebo-controlled pilot study in type 2 diabetic patients, showed that the supplementation of 520 mg of docosahexaenoic acid (DHA) + eicosapentaenoic acid (EPA) fish-oil in the form of 2 soft gels per day for 24 weeks, resulted in a 3.3 cm reduction in waist circumference, compared to baseline values—but not vs. the placebo group—without affecting body weight, BMI and body fat. Furthermore, the supplementation of n-3 PUFA seems to be more effective in the reduction of body fat if associated with regular physical exercise and within the context of low calorie diets, even if the results are not univocal [20, 21].

In conclusion, the overall evidence from RCTs regarding the effect of n-3 PUFA supplementation on body weight reduction is very limited and, if anything, seems to suggest only a small effect on body fat reduction and distribution.

3 Effects on Blood Pressure

High blood pressure (BP) is one of the most relevant independent risk factors for CVDs and the most prevalent all over the world. The major international guidelines have stressed the preventive impact of dietary and life-style intervention in order to reach and maintain optimal BP levels [22, 23]. Given the difficulties in implementing dietary changes, nutraceuticals have been considered a useful option.

3.1 Fiber

The overall body of evidence on the effect of fiber supplements on BP is not very conclusive, at least for some types of fiber. A meta-analysis of 24 RCTs showed that fiber supplementation (11.5 g/day) significantly reduced BP, but did not analyze the effects according to type of fiber [24].

Instead, Evans and colleagues [25], performed a detailed analysis of RCTs focusing on the effects of fiber with different chemical structure, on BP in healthy populations. The authors found that diets rich in β-glucans, provided as oat bran, oat meals or oat beta-glucan-soluble powder—compared with wheat-based control products, reduced systolic blood pressure (SBP) by 2.9 mmHg (95% CI 0.9–4.9) and diastolic blood pressure (DBP) by 1.5 mmHg (95% CI 0.2–2.7), with a median difference in beta-glucans of 4 g, whereas little or no statistical evidence of impact on BP of the other types of dietary fiber was found.

More recently, another meta-analysis of RCTs evaluated the BP effects of different types of viscous fiber supplementation (β-glucan from oat and barley, guar gum, konjac, pectin and psyllium) in healthy and hypertensive individuals [26]. Overall, the results showed that viscous fiber reduced SBP (− 1.59 mmHg) and DBP (− 0.39 mmHg) at a median dose of 8.7 g/day (1.45–30 g/day) over a median follow-up of 7 weeks. Within the fiber types, SBP reductions were observed for psyllium fiber supplementation [− 2.39 mmHg (95% CI − 4.62, − 0.17)], while for beta-glucan, which also has highly viscous properties, only a trend to SBP and DBP reductions was observed. Moreover, hypertensive subjects seem to be more responsive to viscous fiber supplements.

The overall findings demonstrate a modest but significant reduction in SBP and DBP following viscous soluble fiber supplementation, in particular beta-glucans and psyllium.

3.2 Polyphenols

Different studies in humans support the hypothesis that some polyphenols are able to exert favorable effects on BP.

A meta-analysis conducted by Zhang et al. [27] showed that grape seed extracts (100–2000 mg/day), rich in flavonoids, resveratrol and phenolic acids, supplemented for a mean period of 8 weeks can reduce SBP in obese subjects (WMD = −4.469; 95% CI −6.628, −2.310; P < 0.001) and in patients with metabolic syndrome (WMD = −8.487; 95% CI −11.869, −5.106; P < 0.001).

As for flavanol-rich cocoa products, two meta-analyses of RCTs revealed a significant reduction in SBP (−4.5 or −3.2 mmHg, respectively) and DBP (−2.5 or −2.0 mmHg, respectively) following cocoa flavanol intake ranging from 30 to 1000 mg/day in short-term trials of 2–18 week duration [28, 29]. Particularly, the meta-analysis from Ried et al. [29] indicated that the hypotensive effect is present in hypertensive and prehypertensive groups and not in normotensive groups.

A recent meta-analysis showed that in hypertensive patients soy isoflavone intake is associated with reduction in SBP by −5.94 (95% CI −10.55, −1.34 mmHg, P = 0.01) and DBP by −3.35 (95% CI −6.52, −0.19 mmHg, P = 0.04) [30]. As for healthy subjects, daily ingestion of 25–375 mg soy isoflavones (aglycone equivalents) for 2–24 weeks significantly decreased only SBP by 1.92 mmHg (95% CI −3.45, −0.39; P = 0.001) compared with placebo [31].

3.3 Omega-3 Polyunsaturated Fatty Acids (n-3 PUFAs)

There is a wealth of data on the BP-lowering effect of n-3 PUFAs. A recent meta-analysis of 70 RCTs showed that the consumption of omega-3 PUFAs (0.3–15 g/day) for 4–26 weeks reduced SBP by 4.5 mmHg (95% CI −6.1, −2.8) and DBP by 3.0 mmHg (95% CI −4.3, −1.7), in untreated hypertensive individuals [32]. The hypotensive effect is significant also in normotensive individuals, albeit to a more modest extent (SBP −1.25 mmHg; DBP −0.62 mmHg). These results are in line with those from two previous meta-analyses of RCTs showing that omega-3 PUFA supplementation (≥ 3 g/day) for over 2 weeks was associated with an improvement in SBP and DBP [33, 34], again more evident in hypertensive patients. On the other hand, type 2 diabetic patients are not responsive to omega-3 supplementation for what concerns blood pressure [35].

Finally, based on current knowledge, EFSA has established that an intake of about 3 g/day of EPA and DHA are required to obtain the claimed effect on blood pressure.

3.4 Red Yeast Rice, Berberine and Coenzyme Q10

There is very limited evidence in the literature on the effect of red yeast rice (RYR), berberine and coenzyme Q10 on BP. As for RYR, a meta-analysis of RCTs—most of which with low methodological quality—has shown that RYR + conventional therapy has no significant BP-lowering effect compared to placebo + conventional therapy in hypertensive subjects [36].

On the other hand, a meta-analysis of RCTs with berberine suggests that the addition of the latter to lifestyle intervention can be effective in reducing BP (SBP: MD = −5.97 mmHg, 95% CI (−9.19, −2.74), P = 0.0003; DBP: MD = −2.69 mmHg, 95% CI (−5.06, −0.31), P = 0.03) compared to lifestyle intervention alone or placebo [37]. The same positive effect on BP has been observed with berberine + hypotensive drug vs the same hypotensive drug (SBP: MD = −4.91 mmHg, 95% CI (−8.72, −1.1), P = 0.01; DBP: MD = −2 mmHg, 95% CI (−3.76, −0.24), P = 0.03) [37].

Data on the possible effect of coenzyme Q10 on BP are very discordant. In fact, while a previous meta-analysis concluded that coenzyme Q10 has the potential to lower SBP by up to 17 mmHg and DBP by up to 10 mmHg in hypertensive patients [38], a more recent one clearly showed no significant effect either on SBP or DBP when only controlled studies vs placebo (only two studies) were considered [39].

4 Effects on Blood Glucose Levels

Fasting and postprandial hyperglycemia is associated with increasing risk of CVDs and mortality among patients with abnormal glucose metabolism and in healthy population [40–42]. Therefore, treatment strategies to reduce blood glucose either at fasting or in the postprandial state become crucial to reduce the risk of CVDs.

A growing number of nutraceuticals with variable glucose lowering activity have been proposed as a quite novel approach to treat hyperglycemia, although the scientific research on their use has produced conflicting results and the reliability of a number of trials has been flawed by methodological limitations.

4.1 Fiber

Data from clinical trials seem to suggest that soluble fiber supplementation significantly reduces blood glucose levels, especially in the postprandial state, in subjects with prediabetes and in patients with diabetes. The glucose-lowering effect of this type of fiber ranges from 7 mg/dl (for glucomannan) to 45 mg/dl (for psyllium, in the postprandial state), with possible variations in relation to the doses used in the different trials [5, 43–45].

Although most intervention trials with fiber supplements are of short duration and performed on small groups of subjects, the results are quite consistent, especially for β-glucans and pectin. In fact, based on current knowledge, these types of fiber have been the object of a specific claim by EFSA for

the maintenance of optimal postprandial glucose levels at a dosage of 4 g for each 30 g of available carbohydrates for β-glucans, and 10 g for meal for pectin.

4.2 Polyphenols

Epidemiological and clinical studies support the favorable effects of polyphenol-rich diets, characterized by a higher amount of polyphenols from cereals, fruit, vegetables, coffee, tea, and chocolate, in preventing diabetes and in improving blood glucose levels [46–49].

Against this background, in recent years, the possible glucose-lowering effect of different types of polyphenols added to the habitual diet is raising increasing interest. Two metanalysis of randomized controlled trials indicate that flavan-3-ols, present in green tea, green tea extracts, and chocolate, improve glucose metabolism (significant decrease in fasting blood glucose and glycosylated hemoglobin), and that this effect is caffeine-independent and more evident with higher doses of epigallocatechin (from 230 to 1200 mg/day) [50, 51]. Similar effects appear to be present for soy isoflavones. In fact, along the same line, a metanalysis of few intervention studies has shown that soy isoflavones—in particular genistein at 40–160 mg/day—significantly reduce fasting blood glucose and serum insulin although this effect is very limited from clinical point of view and present only in postmenopausal women [52].

A small number of intervention studies evaluated the supplementation of phenolic compounds derived from extra-virgin olive oil and olive leaves, i.e., oleuropein (at a mean dose of 51.1 mg/day) and hydroxytyrosol (at a mean dose of 9.7 mg/day); the results are quite promising, as they show a significant decrease in fasting blood glucose and glycosylate hemoglobin, but the evidence is still too scant for any conclusion to be drawn [53, 54].

Finally, some studies on resveratrol—one of the most studied phenolic compounds, largely present in grape peels—seem to support its hypoglycemic action, showing a decrease in glycemia, hemoglobin and insulin, but only in people with diabetes [55].

In conclusion, although the results of some intervention studies seem to suggest a possible hypoglycemic effect related in particular to some types of polyphenols used as supplements, they must be confirmed by longer-term trials on larger population before recommendations may be given. Actually, up to now no claims have been released for polyphenols regarding the modulation of glucose metabolism.

4.3 Berberine

Berberine is an isoquinoline plant alkaloid present in several plants, used since many years in China for its different therapeutic properties.

To date, studies in type 2 diabetic patients, and metanalysis of these studies show that a dose of berberine between 0.5 and 1.5 g/day for 8–12 weeks reduces fasting and postprandial blood glucose as well as HbA1c either when used alone or in combination with oral hypoglycemic agents [56]. Similar effects have been observed in subjects with metabolic syndrome, in whom berberine administration induced a 36% remission of the presence of metabolic syndrome, decreased waist circumference, systolic blood pressure, TG, glucose levels and insulin secretion, and increased insulin sensitivity [57].

While berberine seems to be effective in improving blood glucose levels, some limitations need to be considered: (1) the evidence comes mainly from studies carried out in Asians, at least for the use of berberine alone, and it is not transferable to other ethnic groups, (2) no data is as yet available on the long-term safety of its use.

In fact, so far, neither EFSA nor FDA has yet released specific claims on the efficacy and safety of berberine.

4.4 Combination of Nutraceuticals

Nutraceutical combinations have been used as therapeutic strategies, especially for patients whose lipid and glucose levels were marginally high, but not to the extent as to warrant the prescription of either lipid- or glucose-lowering medications. A combination of nutraceuticals containing red yeast rice, berberine, policosanol, astaxanthin, Coenzyme Q10 and folic acid has been reported to be effective in reducing glucose levels, although the magnitude of the reduction varied across trials, the difference partly ascribable to different durations and sample sizes of trials exploring lipid- and glucose-lowering effects of such combination [58, 59].

5 Effects on Plasma Lipids

Dyslipidemia, in particular high LDL-cholesterol (LDL-C) concentrations, are considered one of the main CV risk factors [60]. Lifestyle and different drugs are very effective in optimizing lipid profile. However, in some conditions and in some individuals, nutraceuticals as "pharmaceutical-grade nutrients" could represent a potentially useful tools to reduce LDL-C and optimize the overall plasma lipid profile in the general population as well as in people at high CV risk—in the latter cases in addition to the pharmacological therapy.

5.1 Fiber

Pirro et al. recently summarized the evidence from randomized controlled trials, analyzing the results of relevant meta-analyses [61]. The LDL-C-lowering effect of fiber ranges from −6 mg/dl (β-glucan and chitosan) to −22 mg/

dl (guar gum) in both healthy subjects and in patients with either hypercholesterolemia or diabetes. The effect of fiber supplementation on triglycerides (TG) and HDL-cholesterol (HDL-C) is less clear, even if a reduction of TG concentrations (− 11 mg/dl) has been observed for chitosan and glucomannan [61].

Based on current evidence, some fibers obtained a claim by FDA (β-glucan and psyllium) and by EFSA (β-glucan, chitosan, glucomannan, guar gum, hydroxypropylmethylcellulose and pectin) for the maintenance of optimal LDL-C concentrations. EFSA has stated the effectual amount for the specific fibers as follow: β-glucan ≥ 3 g/day, chitosan 3 g/day, glucomannan 4 g/day, guar gum 10 g/day, hydroxypropylmethylcellulose 5 g/day and pectin 6 g/day [61].

5.2 Polyphenol

During the last decades, there has been substantial interest in the potential role of polyphenols in the modulation of lipid metabolism.

The main evidence comes from studies exploring the hypolipidemic effect of cocoa polyphenols (flavan-3-ols). Overall, the results of meta-analyses of randomized controlled trials show that cocoa polyphenols (from 166 to 2110 mg/day) significantly affect LDL-C, HDL-C and TG concentrations although with very limited effects from a clinical point of view [51, 62, 63]. As for tea polyphenols (flavan-3-ols), the current evidence is not conclusive due to the small number of high quality trials and the variability in dosage, exposure and study population [64–68]. However, the overall findings suggest that green tea may have greater effect than black tea, at least on LDL-C concentrations, due to the higher amount of catechins. As a matter of fact, the consumption of green tea beverages or extracts (from 145 to 3000 mg/day of catechins) significantly reduced LDL-C by 2.19 mg/dl [64, 65]. Conversely, similar amounts of black tea failed to show a hypocholesterolemic activity in any of the meta-analyses performed [66, 67]. None of the meta-analyses showed any effect on HDL-C [64–68] or TG concentrations [68].

Looking at other specific phenolic compounds, a recent meta-analyses on quercetin supplementation has shown to significantly reduce LDL-C and TG (− 5 mg/dl and − 7 mg/dl, respectively), and to increase HDL-C concentrations (2 mg/dl) even if these effects might not be clinically relevant [69]. However, a previous meta-analysis showed a meaningful reduction of triglycerides concentrations (− 24.54 mg/dl) when more than 500 mg/day of quercetin were supplemented. Greater effect on LDL-C were observed for anthocyanin supplementation in both healthy [70] and dyslipidemic subjects [71] (− 14 mg/dl and − 22 mg/dl, respectively). Moreover, anthocyanins reduced TG (26 mg/dl) and increased HDL-C (6 mg/dl) in dyslipidemic subjects

[71], whereas no effect on these parameters was detected in healthy subjects [70]. For resveratrol, one of the phenolic compounds mostly studied, the current evidence does not support its hypolipidemic action (with resveratrol doses ranging from 8 mg/day to 1500 mg/day) [72, 73].

Finally, the results of a meta-analyses have shown that isoflavone extracts (on average 15 mg/day) seem to effectively reduce TG concentrations (− 41 mg/dl) in patients with hypercholesterolemia, whereas no variations in LDL-C and HDL-C were observed [74].

Due to the limited clinical evidence, no claims have so far been released for polyphenols for the modulation of lipid concentrations. However, it should be pointed out that hydroxytyrosol and its derivative (oleuropein and tyrosol) have received a claim for the protection of LDL particles from oxidative damage (effective dose 5 mg/day), likely suggesting that polyphenol may exert cardioprotective effects through mechanisms other than modulation of lipoprotein metabolism.

5.3 Omega-3 Polyunsaturated Fatty Acids (n-3 PUFAs)

There is growing evidence supporting the beneficial effects of omega 3 supplementation (2–3 g/day) on TG (− 20 mg/dl on average), particularly among people with more elevated baseline concentrations [75–78]. In some of these intervention studies, the decrease in TG was accompanied by a slight increase in LDL-C [79], while, on the whole, no effect on HDL-C has been consistently reported.

Based on current evidence, omega 3 supplementation (2–4 g/day) is recommended by the main international guidelines for the treatment of hypertriglyceridemia, and in addition to lifestyle changes and statin use in people with TG concentrations ranging from 200 to 500 mg/dl [80]. EFSA released a claim for 2 g/day of EPA and DHA to obtain the maintenance of normal fasting blood concentrations of triglycerides.

5.4 Phytosterols

Clinical studies and meta-analyses have demonstrated that phytosterols consumption (2–3 g/day) induces a mean 10%-reduction of LDL-C in healthy subjects and in patients with hypercholesterolemia and/or diabetes, with little or no effects on HDL-C and TG [61].

Due to the consistent evidence, FDA and EFSA endorsed a claim related to the use of phytosterols for LDL-C reduction. However, EFSA recommended not to exceed a dose of 3 g/day to prevent sitosterolemia (a rare autosomal recessive disease characterized by phytosterol accumulation), and suggests that patients receiving lipid-lowering medications should use phytosterols under medical supervision [61].

5.5 Red Yeast Rice

The hypolipidemic action of monacolin K, a natural analogue of lovastatin produced by the *Monascus purpureus*-fermentation of red rice, has been proven by meta-analyses of clinical trials carried out in healthy subjects and in patients with dyslipidemia, diabetes, coronary heart disease or hypertension [61]. The reduction of LDL-C was − 30 mg/dl on average for a mean monacolin k supplementation of 10 mg/day. With the same amount of monacolin K, an hypotriglyceridemic effect was observed (− 26 mg/dl on average), whereas no influence on HDL-C was detected.

The amount of 10 mg/dl of monacolin K from red yeast rice has received the claim for the maintenance of normal LDL-C concentrations from EFSA and FDA [61].

However, it must be taken into account that monacolin K should have the same restrictions as lovastatin, according to an FDA warning. Moreover, the Joint Commission of Experts of the Federal Office of Consumer Protection and Food Safety and the Federal Institute for Drugs and Medical Devices in Germany have stated that products providing 5 mg/day of monacolin K should be classified as drugs since they have a significant pharmacological action. In this regard, very recently, EFSA has concluded that "the available information on the adverse effects reported in humans was judged to be sufficient to conclude that monacolins from red yeast rice when used as food supplements were of significant safety concern at the use level of 10 mg/day" [81].

5.6 Berberine

To date, evidence of a lipid-lowering effect of berberine comes mainly from studies carried out in Asian populations and cannot be easily extrapolated to other ethnic groups. Nevertheless, the main findings considered in three meta-analyses [61] show that berberine (0.5–1.5 g/day) lowers LDL-C and TG concentrations (on average − 22 mg/dl and 37 mg/dl, respectively), while beneficially increases HDL-C (on average 2 mg/dl).

So far, neither EFSA nor FDA have released specific claims on the efficacy of berberine.

5.7 Soy Protein

Soy protein has been largely investigated, even if it is not easy to evaluate its hypolipidemic effect independently of the isoflavone content. Overall, the evidence suggested that soy protein may improve lipid metabolism, affecting particularly LDL-C, but the extent of these effects is not at all conclusive [61]. Furthermore, soy protein seems to act only in individuals with high baseline LDL-C concentrations for whom other pharmacological therapies are now more indicated.

No claims for soy protein and lipid concentrations have been authorized by EFSA, whereas the claim released by FDA in 1999 is under debate as a result of more recent evidence.

5.8 Coenzyme Q10

In recent years, the coenzyme Q10 (CoQ10) has attracted scientific interest for its possible role on lipid profile.

A meta-analysis of RCTs showed that the consumption of CoQ10 at low doses (< 200 mg/day) significantly reduced serum triglycerides levels by 0.17 mmol/l, without affecting other plasma lipids, in overweight and obese individuals with type 2 diabetes [82]. On the other hand, Sahebkar and colleagues, in a meta-analyses of seven RCTs, suggested a significant lowering effect of CoQ10 supplementation on plasma Lipoprotein-a (Lp(a)) levels, particularly in patients with baseline Lp(a) values ≥ 30 mg/dl. No change in the plasma concentrations of total cholesterol, LDL-cholesterol, HDL-cholesterol and triglycerides was reported in this meta-analysis [83]. Findings from a more recent meta-analysis including eight RCTs showed that taking CoQ10 significantly decreased total cholesterol and increased HDL-cholesterol levels in patients with coronary artery disease (CAD), without any effect on LDL-cholesterol, triglycerides and Lp(a) levels [84].

In conclusion, due to the limited clinical evidence, no conclusive indication can be given about the possible efficacy of coenzyme Q10 supplementation on plasma lipids.

5.9 Combination of Nutraceuticals

The available evidence on the effect of fiber and phytosterol combination has shown a slightly higher cholesterol-lowering action compared to the single components. Conversely, the combination of phytosterols and monacolin K did not provide any additional effect compared to the individual nutraceuticals [61].

A recent meta-analyses focusing on the effect of a nutraceutical comprising monacolin K (3 mg), berberine (500 mg), policosanols (10 mg), astaxanthin (0.5 mg), coenzyme Q10 (2 mg), and folic acid (200 μg) has shown that this combination reduced LDL-C (24 mg/dl) and TG (14 mg/dl), and increase HDL-C concentrations (2 mg/dl) [59].

6 Conclusions

The scientific evidence indicates a possible role of some nutraceuticals in the development of different CV risk factors (Table 1). This is also supported by evidence of the potential beneficial effects of single nutraceuticals and few

Table 1 Summary of the metabolic effects of nutraceuticals on body weight, blood pressure, blood glucose levels and plasma lipids

	Body weight	Blood pressure	Blood glucose levels	Plasma lipids		
				LDL-c	Triglycerides	HDL-c
Fiber	↓ (soluble/viscous fibers)	↓ (soluble/viscous fibers mainly in hypertensive subjects)	↓ (soluble/viscous fibers mainly ß-glucan and pectin)	↓ (soluble/viscous fibers mainly oat β-glucan, psyllium, chitosan, glucomannan, guar gum, HPMC, pectin)	–	–
Polyphenols	↓/– (green tea catechins)	↓ (resveratrol, cacao flavanols, soy isoflavones mainly in hypertensive and obese subjects)	↓ (tea and cacao flavan-3-ols, soy isoflavones, olive oil phenolic compounds, resveratrol)	? (tea and cocoa flavan-3-ols) ↓ green tea catechins	↓ Anthocyanins	–
Omega-3 PUFA	?	↓ (in hypertensive subjects) – (in diabetic subjects)	– (↑ for doses > 4 g/day)	↑	↓↓	–
Phytosterol	NE	NE	NE	↓	–	–
Red yeast rice	NE	?	NE	↓↓		-
Berberine	NE	↓	↓ (in Asian population)	↓ (in Asian population)	↓ (in Asian population)	↑ (in Asian population)
Coenzyme Q 10	NE	?	NE	?	?	?
Soy protein	NE	NE	NE	–/↓ (hyperlipidemic subjects)	NE	NE

↓ Decrease, ↑ increase, – no effect, ? limited and variable data, *NE* not evaluated

red yeast rice based combinations of nutraceuticals on surrogate markers of CV risk, as vascular function [85].

Fiber, mainly the soluble/viscous type, seems to have beneficial effects on different CV risk factors even if the entity of these effects is not very high. Furthermore, LDL-cholesterol levels are beneficially influenced by phytosterol, red yeast rice, and berberine, which seems to act positively also on blood glucose levels, plasma triglycerides, HDL-cholesterol and blood pressure.

The effects of some types of polyphenols on different CV risk factors seem quite suggestive but there is urgent need for very well controlled intervention studies on large populations and for long periods of time, to be sure also of the safety aspect. Indeed, this is true for all nutraceuticals and applies also to the use of nutraceutical combinations. The clinical use of the combination of different nutraceuticals has become widespread, with the aim to act simultaneously on different CV risk factors and on the same risk factor through different mechanisms. However, also for this specific aspect we need to have more scientific evidence deriving from well-controlled intervention studies, as required for drugs.

While awaiting such evidence, we can say that some nutraceuticals may be useful in particular circumstances and in well-identified individuals, i.e. those at low-moderate CV risk who do not yet need drugs, or in addition to drug therapy—in line with what suggested by scientific societies. In any case, nutraceuticals should be taken under medical/nutritionist supervision. This last point is crucial since nutraceuticals, to be effective, should be taken regularly and at the recommended dosage.

Compliance with Ethical Standards

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