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Review

# Food and plant bioactives for reducing cardiometabolic disease: How does the evidence stack up?

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ABSTRACT

*Background:* The cornerstone of cardiovascular disease prevention is a healthy lifestyle. A large body of research indicated a number of food and plant bioactives potentially efficacious in reducing some highly prevalent cardiovascular disease risk factors, such as hypercholesterolemia, hypertension and insulin-resistance.

*Scope and approach:* The aim of this review focuses on reviewing the available data on food and plant components improving lipid level or lipid oxidation, with demonstrated benefit on human vascular health, in particular in regards to endothelial function and arterial stiffness.

*Key findings and conclusions:* Despite the availability of a large number of trials demonstrating short-term lipid-lowering effects of several food and plant bioactives, only a few of them have also demonstrated a direct positive effect for the prevention of vascular aging. In particular, promising data are available as regards green tea extract, red yeast rice, coenzyme Q10, soy, omega-3 polyunsaturated fatty acids, curcumin, and vitamin E. Supplementation with red yeast rice and omega-3 polyunsaturated fatty acids has also been associated with a decrease in cardiovascular mortality risk. Future clinical research will have to focus more on middle term modification of endothelial function and arterial stiffness (markers of vascular aging) rather than on short-term effects using indirect laboratory risk markers.



## 1. Background

Atherosclerosis-related cardiovascular diseases (CVD) are the leading cause of mortality worldwide, and the main cause of death under 75 years old in Western countries (World Health Organization, 2015) with a huge social and economic impact (Bloom et al., 2011).

From the era of the "fathers" of medicine, like Aesculapius, a large attention has given to a correct diet as the best way to maintain the health. In the last century, we have sampled much data on diets or specific diet components that could have positive or deleterious effects on health (Kushner & Sorensen, 2013). In particular, as regards CVD prevention, the first approach has to be focused on a population-based improvement of life-style, based on a low salt and low-energy "healthy Mediterranean diet" (Piepoli et al., 2016). The evidence-based definition of a healthy diet is however not always simple, in particular when based on epidemiological data. In fact, epidemiological data relate the assumption of specific dietary components or specific dietary patterns with the risk of disease development (Cicero & Stallone, 2016). They are the milestones on which we built dietary guidelines and furnish dietary advice. They are particularly relevant when obtained in large population samples followed up for years with a standardized methodology. However, they also have some main limitations (Freedman, Schatzkin, Midthune, & Kipnis, 2011; Patro-Gołąb & Szajewska, 2013): (A) They are population-specific: it is not immediately true that a protective habit for a population is also protective for a different one, because other factors could be involved such as other dietary components, physical activity, environment, genetics/genomics, (B) They are usually "old": in the time the study is carried out (from years to decades) and the data analyzed, the dietary and behavioral habits of the population could have been changed. The typical example is the one of the so called Mediterranean diet, codified on the basis of the South-Italian habits in the '50s, that are totally different from the current ones; (C) They are usually related to a life-long exposition to a specific diet or diet component, so the observation that the life-time exposition to a diet component seems to be protective against the development of

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a disease, does not mean that it will be protective when increased in the diet in the middle-age or elderly age.

For these reasons, recent research has tried to identify bioactive components of foods or plants (Table 1) in order to individualize the mechanisms of actions by which improve CVD risk factors such as LDL-cholesterolemia (Sahebkar et al., 2016), blood pressure (Cicero & Colletti, 2016a) or insulin-resistance (Borghi & Cicero, 2016) and have focused on the experimental verification of these effects in preclinical and clinical models. A part of them have been summarized in Fig. 1.

## 2. Scope and approach

Currently, the relatively large availability of data on food bioactives and nutraceuticals improving CVD risk factors in humans is not sufficient to write reliable guidelines, because data are mainly derived by observational studies and short-term intervention trials. Since it is difficult to plan long-term clinical trials on morbidity and mortality, we could test the middle-term effect of single food bioactives or nutraceuticals on surrogated end-points related to cardiovascular health, such as flow-mediated dilation (Matsuzawa, Kwon, Lennon, Lerman, & Lerman, 2015) or pulse-wave velocity (Vlachopoulos, Aznaouridis, Terentes-Printzios, Ioakeimidis, & Stefanadis, 2012), markers of endothelial reactivity and arterials stiffness, respectively. In this context, for brevity purpose, we have focused our attention on food components and nutraceuticals with demonstrated lipid-lowering effect in humans or antioxidant effect on human LDLs, and are also supported by trials showing a positive effect on instrumental markers of CV health.

A systematic search strategy was developed to identify trials in both MEDLINE (National Library of Medicine, Bethesda, MD; January 1970 to September 2016) and the Cochrane Register of Controlled Trials (The Cochrane Collaboration, Oxford, UK). The terms 'nutraceuticals' 'dietary supplements', 'food bioactive', 'herbal drug', 'hypercholesterolemia', 'dyslipidemia', 'oxidized LDL', 'flow mediated dilation', 'pulse wave velocity', 'endothelial function', 'arterial stiffness', 'intima-media thickness', and 'cardiovascular mortality' were incorporated into an electronic search strategy. The bibliographies of all identified studies and review articles were reviewed to look for additional studies of interest. The authors reviewed all of the citations retrieved from the electronic search to identify potentially relevant articles for this review. We excluded *in vitro* data and animal studies because focusing on human data, in order to limit our report to food components and nutraceuticals for which safety and tolerability in humans are already known. Therefore, we preferentially selected papers reporting recent comprehensive reviews or meta-analyses, or original clinical trials on substance with lipid-lowering effects and improvements for vascular health.

## 3. Red yeast rice

Red yeast rice (RYR) is a nutraceutical obtained by the fermentation of a yeast (usually *Monascus purpureus*) in rice (*Oryza sativa*). RYR contains sugars (25–73%), proteins (14–31%), water (2–7%), fatty acids (1–5%), pigments, sterols, isoflavones and polyketides (Ma et al., 2000). The yeast during the fermentation process enriches the rice through a complex of substances with important lipid-lowering activities including polyketides as monacolins (compactin, monacolins K, M, L, J, X) which have an inhibitory action on 3-hydroxy-3-methyl-glutaryl-CoA (HMG-CoA) reductase (the key enzyme in the endogenous cholesterol synthesis). Usually food supplements derived from RYR contain a concentration of monacolins up to 1.9% (Gordon, Cooperman, Obermeyer, & Becker, 2010).

The lipid-lowering efficacy of RYR has been confirmed by some

**Table 1**
Nutraceutical with best clinical evidence of potential activity on cardiovascular disease risk reduction.

| Nutraceutical | Dosage/day | Effects on laboratory risk markers | Vascular effects | Level of evidence |
|---|---|---|---|---|
| Red Yeast Rice | 5-10 mg (Monacolin K) | ↓ LDL-C, ApoB, hsCRP, MMP2, MMP9 | ↑ FMD, ↓ PWV. ↓ CV events in secondary prevention | Meta-analysis of RCTs |
| Berberine | 500-1500 mg | ↓ LDL-C, ApoB, TG, hsCRP, IL-6, Adhesion molecules, MMP-9, Glucose, HbA1c, HOMA-index | ↓ Blood pressure | Meta-analysis of RCTs |
| Curcumin | 1-2 gr | ↓ LDL-C, TG, Lp(a), Glucose, HbA1c, HOMA index, Leptin, hsCRP, TNF-alpha, IL-6, ↑ Adiponectin, HDL-C | ↑ FMD, ↓ PWV | RCTs (discordant data) |
| Omega-3 polyunsaturated fatty acids | 1-4 gr | ↓ sdLDL, TG, hsCRP, TNF-alpha, Adhesion molecules, ↑ Omega 3 index | ↓ Blood pressure, ↑ FMD, ↓ PWV, ↓ cardiovascular mortality (epidemiological data), ↓ post-myocardial infarction sudden death risk | Meta-analysis of RCTs |
| Coenzyme Q10 | 50-600 mg | Unclear | ↓ Major CV events and total mortality | RCTs |
| Green Tea | 25-100 gr | ↓ LDL-C, oxLDL | ↓ Blood pressure, ↑ FMD, ↓ PWV (tea) | Meta-analysis of RCTs |
| Cocoa polyphenols | 100-800 mg | ↓ oxLDL, TG, Glucose, HbA1c, HOMA index, ↑ Adiponectin, HDL-C, NO | ↓ Blood pressure, ↑ FMD, ↓ PWV | Meta-analysis of RCTs |
| Anthocyanins from fruits | 100-450 mg | ↓ oxLDL, TG, Glucose, HbA1c, HOMA index, ↑ Adiponectin, HDL-C | Not demonstrated | RCTs |
| Grape | 340 mL grapefruit juice/day (210 mg naringenin glycosides) | Anti-oxidant | ↓ PWV | RCT |
| Quercetin | 100-162 mg | ↓ oxLDL, vasorelaxant | ↓ Blood pressure, ↑ FMD | RCTs |
| Soy and Lupin | 25-100 gr | ↓ LDL-C, ApoB, ↑ NO | ↑ FMD, ↓ PWV (soy with isoflavones), ↓ blood pressure | Meta-analysis of RCTs |
| Vitamin E | 400-800 UI | ↓ LDL-C, ApoB, oxLDL, ↑ HDL-C | ↑ FMD, ↓ PWV, ↓ risk of myocardial infarction | Meta-analysis of RCTs (discordant data) |
| Beta-carotene | 15-50 mg | Anti-oxidant | No clear effect | Meta-analysis of RCTs |
| Vitamin C | 120-500 mg | Anti-oxidant | No clear effect | Meta-analysis of RCTs |

ApoB = Apolipoprotein B, CV= Cardiovascular, FMD= Flow-Mediated Dilation, HbA1c = Glycated Haemoglobin, HDL= High Density Lipoprotein Cholesterol, hsCRP = high sensitivity C-reactive protein, IL-6 = Interleukine-6, LDL-C = Low Density Lipoprotein Cholesterol, MMP = Matrix MetalloProteinases, ox-LDL = oxidized Low Density Lipoproteins, PWV= Pulse Wave Velocity, TNF-alpha = Tumor Necrosis Factor alpha.

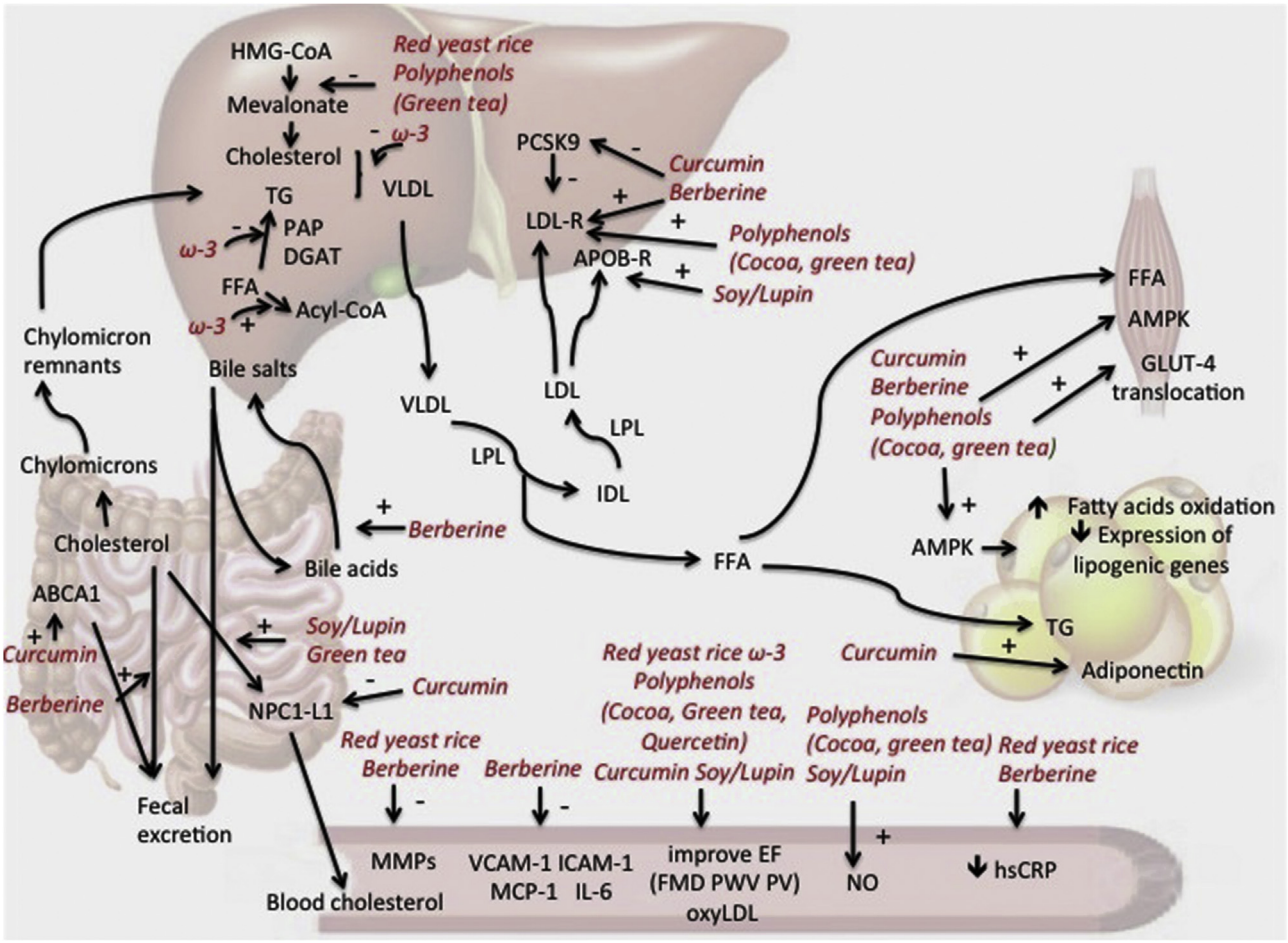


**Fig. 1.** Example of mechanisms of action by which plant bioactives and nutraceuticals may improve cardiometaboli risk in humans.

meta-analyses of randomized clinical trials (RCTs): the most recent one has included 20 clinical trials evaluating the efficacy and safety profile of this nutraceutical. The results showed that (after 2–24 months) RYR reduced low-density lipoprotein cholesterol (LDL-C) on an average of 1.02 mmol/L (−1.20; −0.83) compared to placebo, not different from old statins (pravastatin 40 mg, simvastatin 10 mg, lovastatin 20 mg) (0.003 mmol/L (−0.36; 0.41)). In addition, a small increase of high-density lipoprotein cholesterol (HDL-C) (0.007 mmol/L (0.03; 0.11)) and a decrease of triglycerides (TG) (−0.26 mmol/L (−0.35; −0.17)) compared to placebo were observed. The doses of RYR used were different and vary from 1200 mg to 4800 mg/day containing from 4.8 mg to 24 mg of monacolin K (MonK). Concerning the safety profile, the risk of developing muscular side effects was lower in RYR groups (0–23.8%) compared to control groups (0–36%). There were no cases of rhabdomyolysis or myopathy with creatine kinase (CK) levels increased more than 10 times the upper limit (Gerards, Terlou, Yu, Koks, & Gerdes, 2015).

RYR not only reduces LDL-C, but also improves endothelial function in humans. In a RCT involving 50 patients with coronary heart disease (CHD), treated with 1200 mg/day of RYR or placebo for a period of six weeks and following a high fat intake (50 g) meal, the levels of high sensitivity C-reactive protein (hs-CRP), the flow mediated dilatation (FMD) (at 0 and 4 h) and the lipid parameters were monitored. The results showed that the group treated with RYR at the end of the sixth week obtained a reduction in levels of hs-CRP and triglycerides area under the curve (TG-AUC) ($p < 0.001$ for each), in addition to an improvement of postprandial and preprandial FMD ($p < 0.001$). There were no significant changes in serum lipids and FMD in the placebo group (Zhao et al., 2004).

These results were then confirmed in a double-blind study involving 40 moderately hypercholesterolaemic and non-smokers subjects, treated with 10 mg of MonK or placebo. At the end of the fourth week of treatment, the endothelial function (pulse volume (PV) after monacolin treatment: +6.0%; after placebo: −0.3%, $p < 0.05$) and arterial stiffness (pulse wave velocity (PWV) after monacolin treatment: −4.7%; after placebo: +1.1%, $p < 0.05$) improved significantly only in the monacolin group (Cicero et al., 2016). These data could be also related to the observed reduction in the level of matrix metalloproteinases (MMPs) in humans treated with RYR compared to placebo, in particular for MMP-2 (−28.05%) and MMP-9 (−27.19%) (Cicero et al., 2013).

RYR use is a rare example of nutraceutical studied using hard outcomes. RYR supplementation has in fact shown relevant efficacy in reducing CVD risk in adult and elderly patients in secondary prevention. In particular, in a large trial involving 66 hospitals in China, 4780 patients (1445 aged between 65 and 75 years) with a history of myocardial infarction were randomized into two groups (placebo and RYR) and followed for a mean of four years. The results showed that patients in the RYR group benefited from a reduction in the risk of coronary heart disease (31.0%, $p = 0.04$), all-cause mortality (31.9%, $p = 0.01$), stroke (44.1%, $p = 0.04$), the need for

artery bypass graft or a percutaneous coronary intervention (48.6%, p = 0.07) and malignancies (51.4%, p = 0.03). It has also been estimated that following a RYR treatment for four years, the number needed to treat (NNT) to prevent one coronary event, one coronary death and one mortality due to all causes in elderly patients were respectively 18, 33 and 23. In adults however at the same time were 23, 82 and 51. Side effects (dyspepsia, CPK increase, myalgia) were not significantly different in placebo and RYR treated patients (Ye et al., 2007).

While the chronic intake of high doses of monacolins (>10 mg/day) could be responsible for the mild to moderate severity of side effects (CPK increase, myalgia), lower dosages are usually well tolerated (Cicero, Derosa, & Borghi, 2010). However, serious attention must be made to citrinin, a mycotoxin metabolite derived from the fermentation of *Monascus*. EFSA (European Food Safety Authority) has expressed as 0.2 μg/kg b.w. per day the highest quantity of citrinin assumable in humans with no nephrotoxic effects (EFSA, 2012). However, at these doses genotoxic and carcinogenic effects are not excluded (Gordon et al., 2010).

For safety reasons, RYR is currently used in clinical practice also at low doses in combination with other nutraceuticals in order to reduce the daily dose of MonK (and thus their potential side effects, in particular the muscular ones). The aims are also to exploit the pleiotropic effects of the other nutritional supplements or simply to increase the overall lipid-lowering effect.

A recent meta-analysis of 14 RCTs including data from 3159 subjects showed that the association of RYR and berberine (another lipid-lowering plant active described in the next chapter) improved the plasma level of TC by −0.68 mmol/L (p < 0.001), LDL-C by −0.61 mmol/L (p < 0.001), HDL-C by 0.07 mmol/L (p < 0.001), TG by −0.16 mmol/L (p < 0.001) and glucose by −0.14 mmol/L (p = 0.010), and these effects appeared to be maintained in the long term (Pirro et al., 2016). Moreover, this nutraceutical combination improved the leptin-to-adiponectin ratio, whereas adiponectin levels were unchanged (Ruscica et al., 2014), contrarily to what usually observed with statins (Arnaboldi & Corsini, 2015). Endothelial function and PWV were improved by the association of red yeast rice and berberine in dyslipidaemic patients as well (Cicero, Parini, et al., 2013).

RYR was combined also with plant sterols, artichoke and silymarin obtaining comparable results on the reduction of cholesterolemia and inflammatory markers. Nevertheless, the levels of efficacy and reduction of CV risk of these single components are still unclear and should be investigated (Cicero & Colletti, 2016b).

Supplementation with RYR (10 mg MonK) and Coenzyme Q10 (30 mg) was tested in a RCT carried out on 25 healthy, mildly hypercholesterolaemic subjects. At the end of the fourth week, monacolins-treated patients experienced a more favorable percent change in TC (−12.45%, 95%CI: −16.19; −8.71), LDL-C (−21.99%, 95% CI: −26.63; −17.36), non-HDL-C (−14.67%, 95%CI: −19.22–10.11), MMP-2 (−28.05%, 95%CI: −35.18; −20.93), MMP-9 (−27.19%, 95% CI: −36.21; −18.15), and hs-CRP (−23.77%, 95%CI: −30.54; −17.01) compared to placebo (Cicero, Derosa, et al., 2013). The same combination was then evaluated in 40 moderately hypercholesterolaemic subjects: after 6 months of active treatment, the results showed a more favorable percentage change in LDL-C (−26.3%; p < 0.05), endothelial reactivity (pulse volume displacement: +6.0%; p < 0.05) and arterial stiffness (PWV: −4.7%; p < 0.05) (Cicero, Morbini, et al., 2016).

In conclusion, RYR is an example of nutraceutical with positive effect on hard outcomes such as morbidity and mortality in humans. The tollerability of RYR is very good when patients with myopathies or previous statin intolerance begin the treatment with low dosages.

## 4. Berberine

The discovery of the lipid-lowering activity of berberine (BBR) is relatively recent. BBR is a quaternary benzylisoquinoline alkaloid contained in the rhizome, root, stem, fruit and bark of different species of plants as Hydrastis, *Coptis* and *Berberis* (Liu, Zheng, Zhang, & Long, 2016). BBR is an inhibitor of proprotein convertase subtilisin/kexin type 9 (PCSK9) through the ubiquitination and degradation of hepatocyte nuclear factor 1 alpha, causing an increased level and a limited degradation of hepatic LDL receptor (LDL-R). This mechanism suggests a possible combination with RYR or statin therapy that determine an increase of the PCSK9 levels (an undesirable indirect effect). Being PCSK9 also involved in TG and Lp(a) metabolism and in insulin-resistance, its inhibition could contribute to a larger number of metabolic effects than the simple LDL-C reduction (Ferri & Ruscica, 2016).

Moreover, BBR acts directly on the expression of LDL-R, causing an up-regulation of the receptors through a post-transcriptional mechanism that stabilizes their mRNA (activation of extracellular signal regulated kinases (ERK) and jun amino-terminal kinases (JNK) dependent pathways) (Abidi, Zhou, Jiang, & Liu, 2005;; Li et al., 2009).

BBR could also reduce the intestinal absorption of cholesterol, increasing the faecal excretion and promoting the hepatic cholesterol turnover and the formation of new bile acids (Li, Zhao et al., 2015). Furthermore BBR is an inhibitor of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase-mediated oxidative stress and an activator of 5′ AMP-activated protein kinase (AMPK), which determines an increase in fatty acid oxidation, a reduction of the expression of lipogenic genes and an increase in insulin-sensitivity (Kim et al., 2009; Qiang et al., 2016).

BBR bioavailability is lower than 1%: this is due to several factors including the formation of particle aggregates that precipitate and don't dissolve in the intestinal lumen, the low permeability of the molecule and the intestinal first-pass metabolism (probably of enzymatic origin by CYP2D6 and CYP3A4) which determine a reduction of BBR hematic concentration. Absorbed BBR is substrate of efflux pump P-glycoprotein (P-gp), and that undergoes a hepatic first-pass metabolism. For these reasons, biopharmaceutical strategies (either through the use of enhancers of permeability, either P-gp inhibitors and/or non-conventional pharmaceutical forms) and research on the structure–activity relationship of the molecule are ongoing in order to improve the bioavailability of BBR and attempt to discover new chemical entities structurally similar to BBR, but with a better pharmacokinetic profile.

The lipid-lowering efficacy of BBR has been confirmed by a recent meta-analysis that included 27 clinical trials with 2569 participants. The effects of BBR on lipids were: TC: MD = −0.66 mmol/L (95%CI -1.02; −0.31, p = 0.0002), TG: MD = −0.39 mmol/L (95%CI -0.59; −0.19, p = 0.0001); LDL-C: MD = −0.65 mmol/L (95%CI -0.75; −0.56), p = 0.00001; HDL-C: MD = 0.07 mmol/L (95%CI 0.04; 0.1, p = 0.00001). These effects seem to be additive to the effect of statins and are associated with a positive impact on glucose metabolism and blood pressure as well. Side effects were mild to moderate, mostly gastrointestinal (constipation, diarrhoea, abdominal distension) and comparable to the control groups (Lan et al., 2015).

BBR has shown a significant efficacy also in patients in secondary prevention for CVD: 130 patients undergoing percutaneous coronary intervention (PCI), randomized into two groups and treated with BBR (600 mg/day) or placebo in addition to standard therapies. The results showed a marked reduction in the levels of TG (−26%, p < 0.001 vs. baseline, even if the difference vs. placebo did not reach statistical significance due to large inter-individual

variations) and LDL-C (−24%, $p < 0.001$ vs. baseline). In addition, both groups have benefited from a reduction in the levels of monocyte chemoattractant protein-1 (MCP-1) and interleukin 6 (IL-6) ($p < 0.05$ for each), as well as hs-CRP, vascular cell adhesion molecule-1 (VCAM-1), intercellular adhesion molecule-1 (ICAM-1), MMP-9 ($p < 0.001$ for all) compared to baseline. The levels of MMP-9, ICAM-1 and VCAM-1, after one month were significantly reduced to a greater extent in the BBR group compared to the control and baseline ($p < 0.05$). Side effects were comparable between the two groups: only three patients stopped BBR treatment due to abdominal pain, rash, and constipation. No significant differences were detected in the levels of alanine transaminase (ALT), aspartate transaminase (AST), and creatinine between the two groups, indicating that the BBR should not have negative effects on kidney and liver (Meng et al., 2012). The observed effect of BBR on adhesion molecules is of particular interest considering the recent results of the Heart and Soul study, showing that the serum level of these adhesion molecules is a significant predictor of CV outcomes in patients with stable coronary artery disease (Park et al., 2015).

Some clinical trials have also tested BBR in combination with other nutraceuticals including RYR (as previously mentioned) and silymarin to investigate if the association with RYR could achieve a greater reduction of cholesterolaemia. The association with silymarin has primarily a biopharmaceutical rational (being silymarin an inhibitor of P-gp) to improve BBR bioavailability (Derosa et al., 2013).

In conclusion, the use of BBR is indicated both in primary and secondary prevention especially in slightly/moderately hypercholesterolemic, diabetic and metabolic syndrome patients. The dosages used in clinical practice vary from 500 to 1500 mg/day, with good efficacy on inflammatory markers and tolerable side effects (Derosa et al., 2012).

## 5. Omega-3 polyunsaturated fatty acids

Omega-3 (w-3) are polyunsaturated fatty acids (PUFA) present both in plants (algae, walnut, flaxseed, clary sage, edible seeds, seed) and animal (fish, squid, krill, egg) sources. However, unlike the plants, animals are not able to synthesize w-3. Structurally w-3 contain a double bond in position 3 at the end of the carbon chain (EFSA, 2009). In recent years, the American Heart Association (AHA) and the European Food Safety Agency (EFSA) have recognized the w-3 as preventive nutraceuticals in the development of CVD. In particular, the intake of at least 2 g/day of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) is able to maintain the normal blood levels of TG (EFSA, 2010; Miller et al., 2011).

EFSA health claims and the declaration of AHA are supported by a large number of RCTs. A meta-analysis of Eslick et al. has involved 47 RCTs and 16511 subjects with hypercholesterolemia to assess the effects of the average daily dose of 3.25 g of EPA/DHA for 24 weeks. The results showed a significant reduction in TG of 14% (−0.34 mmol/L (95% CI: −0.41; −0.27)) without relevant effects on other lipid fractions. Reported side effects were not serious, of the mild gastrointestinal type (Eslick, Howe, Smith, Priest, & Bensoussan, 2009). Similar results were obtained in normolipidemic and borderline subjects: the meta-analysis by *Leslie* et al. has included 2270 individuals with optimal lipid or sub-optimal (TG < 177 mg/dL) profiles. A dose-dependent TG reduction of 4–51% was found with doses from 1 to 5 g/day of w-3 (Leslie, Cohen, Liddle, Robinson, & Ma, 2015).

Furthermore the administration of DHA or EPA as individual components, has highlighted a comparable reduction in the levels of TG although DHA showed a modest activity in the reduction of LDL-C (−5%) and an improvement in HDL-C compared to EPA (no significant changes) (Wei & Jacobson, 2011).

The TG lowering effect of w-3 is mediated by a number of mechanisms among which the reduction of the activity of triglyceride-synthetizing enzymes (phosphatidic acid phosphohydrolase or diacylglycerol acyltranferase), the reduction of hepatic VLDL synthesis, the reduction of available substrate for TG synthesis, the increase of fatty acids β-oxidation, the reduction of the endogenous fatty acid synthesis and the increase of phospholipids synthesis (Harris & Bulchandani, 2006).

Beyond some contrasting clinical results, mainly related to the use of non-standardized w-3 extracts and/or different dosages or pharmaceutical formulations (Cicero, Morbini, & Borghi, 2015), the consumption of PUFAs is associated with an improvement of FMD, PWV, cardiovascular disease related mortality and, with larger dosages, to positive effects on inflammatory diseases and mood (Cicero, Reggi, Parini, & Borghi, 2012).

Not all w-3 are the same and not all have shown clear results in the prevention of cardiovascular risk. For example controversial results were observed with alpha-linolenic acid (ALA), which is present in many vegetable oils (as olive and flaxseed oil). A rich source of ALA is the flaxseed (*Linum usitatissumum,* ALA = 50–62% of flaxseed oil or 22% of whole flaxseed), an oilseed crop grown on all continents: the consumption of flaxseed showed a reduction of LDL-C (−0.08 mmol/L). Nevertheless, this effect may be explained by the lignans (0.2–13.3 mg/g flaxseed) and soluble fibers (25% of total weight) present in flexseed that could enhance the final reduction of cholesterol. The cholesterol-lowering effects were more significant in females (in particular in postmenopausal women) and in individuals with high cholesterol levels at baseline (Pan, Yu, Demark-Wahnefried, Franco, Lin, &., 2009). Flaxseed also seems to exert a mild but significant antihypertensive effect (Ursoniu et al., 2016). The available data suggest that the consumption of flaxseed is safe and well tolerated.

Another source of w-3 is the krill (*Euphausia superba),* a crustacean that lives in the Antarctic Ocean, containing many types of long-chain PUFAs (Cicero & Colletti, 2015). The w-3 present in krill oil (EPA + DHA) appear to have a better bioavailability than those found in fish oil: this is possible through the phosphatidylcholine, (one of the major phospholipids present in krill (40%)) which confers a greater stability to fatty acids in the gastrointestinal tract. Moreover, krill oil is rich in antioxidants including astaxanthin and vitamin E. *Ulven* et al. have shown that the effects in the reduction of TG of a dose of 543 mg of DHA and EPA contained in krill oil are comparable to doses of 2.66 g of EPA and DHA present in fish oil (Ulven et al., 2011). Similar data have been subsequently confirmed by *Cicero* et al. (Cicero, Rosticci, et al., 2016), but more trials are need to clearly define the advantage to use krill oil in spite of other w-3 sources.

Finally, w-3, in particular EPA and DHA, represent a nutritional supplement able to reduce triglyceridaemia (−18/25%) but their activities on LDL-C, TC and HDL-C are clinically insignificant. All the PUFAs meta-analyses conducted to date do not report relevant side effects, which are mostly mild or moderate in severity (frequent fishy aftertaste and rare abdominal discomfort). Moreover, a large part of the CV protective effect of w-3 could not be simply related their plasma lipid improving effect, but alto to a large number of biological activities among which the antiproarrhytmic, the antinflammatory and the atheromasic plaque stabilizing ones, demonstrated in several large long-term randomized clinical trials (Cicero et al., 2012; Derosa et al., 2012).

## 6. Coenzyme Q10

Another substance with significant clinical evidence in the context of CVD management is Coenzyme Q10 (CoQ10), often used in combination with RYR to reduce its potential muscular side

effects (Cicero, Morbini, et al., 2016). CoQ10 is an organic molecule which is composed of a lipophilic core (benzoquinone) and an isoprenoid side chain. Dietary sources include red meat, eggs, fish, soy, vegetable oils and wheat germ and as nutritional supplements. It is present ubiquitously in the body, especially in the mitochondria of muscle cells, in both oxidized (ubiquinone) and reduced (ubiquinol) forms and plays a key role in oxidative phosphorylation and ATP synthesis (Yamamoto, 2016).

Beyond the positive effects of CoQ10 on lipid levels and lipid oxidation, it can play a main role in the prevention and treatment of heart failure (HF). In fact patients with advanced HF also have lower myocardial Q10 levels, when compared with patients with earlier HF stages. The reason probably lies in the mechanisms of action of CoQ10 as an antioxidant, a reductor of oxidative stress, an inductor of ATP synthesis and a stabilizer of calcium-dependent channels (Onur et al., 2015).

Clinical evidence suggests that the supplementation of CoQ10 improves some parameters of HF, such as ventricular ejection fraction, left ventricular diameter in addition to improving the quality of life (measured with the six-minutes walking test (6MWT)). In general, improvements in ejection fraction (EF), obtained with CoQ10 dosages from 60 to 200 mg/day, varied from 3.7% ($p < 0.001$) (Fotino, Thompson-Paul, & Bazzano, 2013;; Sander, Coleman, Patel, Kluger, & White, 2006) to 92% ($p < 0.0001$) (Soja & Mortensen, 1997): more pronounced improvements were obtained in subjects with EF>30% compared to patients with EF<30%. This probably suggests that it is important to intervene in the early stages of heart failure. Also the cardiac output, stroke volume, cardiac index and the diastolic volume index were significantly improved.

Certainly the most significant result came from the Q-SYMBIO study, a multicenter randomized placebo-controlled trial which assessed the impact of the administration of CoQ10 (300 mg/day) in 420 patients with moderate or severe HF (for a period of 2 years), not only on CV surrogate endpoints but also included total mortality. People in treatment with CoQ10 have benefited from a significant reduction in Major Adverse Cardiac Events (MACE: 15% CoQ10 vs. 26% placebo, hazard ratio: 0.50; 95%CI: 0.32 to 0.80; $p = 0.003$), CV mortality (9% vs. 16%, $p = 0.026$), all-cause mortality (10% vs. 18%, $p = 0.018$) and incidence of hospital stays for HF ($p = 0.033$) (Mortensen et al., 2014).

A limitation of CoQ10 is its low oral bioavailability: however special delivery strategies (as nanoemulsions, microencapsulation, micelles, complexation with ciclodextrins) and the administration in a fed state (during a high-fat meal) has improved its intestinal absorption (Kumar, Rao, Kumar, Mahant, & Nanda, 2016).

In conclusion, CoQ10 is another example of nutraceutical with positive effect on hard outcomes such as morbidity and mortality in humans with not knonw side effects.

## 7. Curcumin

Curcumin is the most important phenolic compound present in the turmeric spice (curcuminoids constituite approximately the 5% of weight of the rizhome of *Curcuma longa*), consisting of two methoxyphenol rings connected by a conjugated heptadienedione chain. Curcumin is unstable at physiological pH and rapidly degrades in an autoxidation reaction to a major bicyclopentadione product in which the 7-carbon chain has undergone oxygenation and double cyclization. Early degradation products (but not the final bicyclopentadione) mediate topoisomerase poisoning and possibly many other activities of curcumin, among which is associated with different properties including antioxidant, insulin sensitizer, lowering plasma cholesterol and anti-inflammatory effects (Gordon, Luis, Sintim, & Schneider, 2015).

There are many hypotheses about the lipid-lowering mechanisms of action of curcuminoids (which remain unclear): nevertheless, it seems that curcumin increases the efflux of cholesterol via expression of ATP-binding cassette transporter (ABCA1) and activating AMPK-SIRT1-LXRα signaling in THP-1 macrophage-derived foam cells (Liu et al., 2015), inhibits the expression of Niemann-Pick C1-Like 1 (NPC1L1) transporter via sterol regulatory element binding protein-2 (SREBP2) transcription factor (Kumar et al., 2011). Moreover, curcumin enhances cell-surface LDL-R level and promotes LDL uptake through the down-regulation of the expression of PCSK9 (Tai et al., 2014). In addition, epigenetic modulators such as microRNAs (miRs) have emerged as novel targets of curcumin (Momtazi, Derosa, Maffioli, Banach, & Sahebkar, 2016).

However, the results of RCTs regarding the effects of curcumin on lipid profile are still unclear (Sahebkar, 2014). A recent trial including patients with metabolic syndrome, the treatment with 1 g/day of curcuminoids in addition to standard therapy resulted in a significant reduction of LDL-C (−0.78 mmol/L, $p < 0.001$), TG (−0.2 mmol/L, $p = 0.006$), TC (−0.65 mmol/L, $p < 0.001$), Lipoprotein (a) levels (−0.286 μmol/L, $p < 0.001$) and an improvement of HDL-C (0.18 mmol/L, $p = 0.003$) (Yang et al., 2014). These data were later confirmed in another study of 100 patients with metabolic syndrome (Panahi, Khalili, Hosseini, Abbasinazari, & Sahebkar, 2014) and in one on 80 non-alcoholic fatty liver disease patients (Rahmani et al., 2016). In a recent clinical study, the supplementation with curcumin (1 g/day) was associated with a reduction of serum uric acid ($p < 0.001$) (Panahi, Kianpour et al., 2016) and, in another one, with an increase of adiponectin (+76.78%, $p = 0.0330$) levels and a reduction of leptin (−26.49%, $p = 0.238$) (Panahi, Hosseini et al., 2016). All of these effects seem to be related to the main metabolic effect of curcumin, which is an improvement in insulin-resistance (Derosa, Limas, Mac, í, as, Estrella, & Maffioli, 2014): in fact, in another RCT that included 240 pre-diabetic subjects treated for 9 months with an extract of curcumin or placebo, the curcumin group has benefited from a regression of the clinical picture with an improvement of adiponectin, C-peptide, homeostatic model assessment for insulin resistance (HOMA-IR), homeostatic model assessment for β-cell function (HOMA-β) values (Chuengsamarn, Rattanamongkolgul, Luechapudiporn, Phisalaphong, & Jirawatnotai, 2012).

As reported in recent meta-analyses of RCTs, curcuminoids showed an increase in serum activities of superoxide dismutase ($p = 0.0007$) and catalase ($p = 0.005$), glutathione concentrations ($p = 0.01$) and a reduction in serum lipid peroxides ($p = 0.008$) (Panahi, Hosseini et al., 2016) and of TNF-α (Sahebkar, Cicero et al., 2016). This suggests a strong antioxidant and antinflammatory effect of curcuminoids ~~that,~~ with an insulin-resistance improving effect, that may explain its positive effect on FMD (Nakayama et al., 2014) and PWV (Chuengsamarn, Rattanamongkolgul, Phonrat, Tungtrongchitr, & Jirawatnotai, 2014).

In general, the administration of curcumin is well tolerated and the safety profile is good: nevertheless, an important problem is its oral bioavailability. Curcumin has low solubility in water and it is a substrate of rapid gastric and intestinal metabolism. New strategies of release have been studied and tested such as the phytosomal complexation with phosphatidylcholine, using turmeric oleoresin, and the co-administration of piperine, reducing particle size, changing formulation (nanoemulsion, solid lipid nanoparticle, microencapsulation) (Rahimi, Nedaeinia, Sepehri Shamloo, Nikdoust, & Kazemi Oskuee, 2016): however data in *vivo* on these new formulation are yet lacking.

In summary, curcumin represents an antioxidant nutraceutical with multiple actions in CV prevention. It is particularly indicated in patients with insulin-resistance related conditions.

## 8. Green tea, cocoa and other polyphenol sources

Observational studies have suggested the association between the intake of flavonoids and a decreased risk of CVD. A systematic review of prospective cohort studies showed that the intake of anthocyanidins (RR 0.89, 95% CI 0.83, 0.96), proanthocyanidins (RR 0.90, 95% CI 0.82, 0.98), flavones (RR 0.88, 95%CI 0.82, 0.96), flavanones (RR 0.88, 95%CI 0.82, 0.96) and flavan-3-ols (RR 0.87, 95% CI 0.80, 0.95) were inversely associated with the risk of CVD when comparing the highest and lowest categories of intake. In particular, the summary RR for CVD for every 10 mg/day increment in flavonol intake was 0.95 (95% CI 0.91, 0.99) (Wang, Ouyang, Liu, & Zhao, 2014).

Several RCTs emphasize that the consumption of green tea represents a possible tool in the prevention of CVD (Sahebkar, Serban, et al., 2016). In fact, green tea extract is particularly rich in polyphenols (providing up to 35% of the dry weight of the extract), including catechins structurally flavan-3-ols. The most important flavan-3-ol present in green tea extract is epigallocatechin-3-gallate (EPCG) a powerful cardioprotective antioxidant. The polyphenols seems to be responsible for a reduction of lipid peroxidation, determining a qualitative reduction of oxidized LDL. In addition, green tea is an activator of AMP-activated protein kinase (AMPK, which determines an increase of lipogenesis) and an inhibitor of HMG-CoA reductase and interferes with the micellar solubilisation and absorption of endogenous cholesterol. Finally, catechins have reported an enhancer action on the expression of hepatic LDL-R and an inhibitory activity on the ileal apical sodium-dependent bile acid transporter, increasing the biliary excretion of cholesterol (Way et al., 2009; Shishikura, Khokhar, & Murray, 2006).

A meta-analysis of 20 RCTs and 1536 participants showed a reduction of LDL-C (MD: −0.19 mmol/L; 95% CI: −0.3; −0.09, $p = 0.0004$). The tested daily doses ranged from 250 to 1200 mg of green tea extract or from 170 to 850 mg of EPCG (Onakpoya, Spencer, Heneghan, & Thompson, 2014). The lipid-lowering effects of green tea were found to be greater in RCTs with longer durations of intervention. Moreover, green tea extract exerts a mild but significant antihypertensive effect. Green tea is also associated with an improvement of FMD (Park et al., 2010) and PWV (Lin et al., 2016), with no apparent effect on hsCRP levels (Serban, Sahebkar, Antal, Ursoniu, & Banach, 2015). Therefore, overall the consumption of tea is associated to a significant decrease in the risk of CVD morbidity and mortality (Zhang et al., 2015). Side effects of green tea are usually minor and well tolerated: in some RCTs they have reported cases of rash, mild gastrointestinal disorders and transient elevation of blood pressure (Onakpoya et al., 2014).

Randomized clinical trials also show that black tea, usually containing less catechins than green tea, is also able to exert a mild but significant blood pressure lowering effect in humans, which could positively affect the cardiovascular risk profile (Hodgson et al., 2012).

Some meta-analyses of RCTs have highlighted the potential role of the cocoa polyphenols in prevention of CV risk. In particular, the intake of cocoa flavanols (88–800 mg/day) showed beneficial effects on vascular elasticity, improving PWV, FMD, arteriolar and microvascular vasodilator capacity, inflammatory markers (including C-reactive protein and vascular cell adhesion molecules) and the synthesis of nitric oxide (NO) and reducing total peripheral resistance. These effects were observed not only in healthy subjects but also in smokers, diabetic, overweight, hypertensive and elderly patients (Tomé-Carneiro & Visioli, 2016).

In a double blind placebo controlled trial, 100 healthy subjects were treated with 900 mg/day of cocoa flavanols or placebo. At the end of one month cocoa flavanols decreased systolic and diastolic blood pressure by 4.4 mmHg (95% CI: 7.9–0.9 mmHg) and 3.9 mmHg (95% CI: 6.7–0.9 mmHg), PWV by 0.4 m/s (95% CI: 0.8–0.04 m/s), LDL-C by 0.17 mmol/L (95%CI: 0.32–0.02 mmol/L), whereas HDL-C increased by 0.10 mmol/L (95% CI: 0.04–0.17 mmol/L) (Sansone et al., 2015). Similar results were obtained by *Ferri* et al. (Ferri et al., 2015).

In addition to cocoa, also other polyphenol-rich foods as grape, apple, olive oil, green coffee, berries (especially blueberries, blackberries and red fruits), pomegranate and onions could exert a preventive activity towards cardiovascular disease, especially improving blood pressure, dyslipidaemia and endothelial function. Nevertheless, in many types of these nutraceuticals there are specific kinds of flavanoids, the anthocyanins, which have demonstrated antioxidant, anti-inflammatory and lipid-lowering effects (Wallace, Slavin, & Frankenfeld, 2016).

In 58 diabetic patients, 320 mg/day of anthocyanins for 24 weeks significantly increased HDL-C (+19.4%, $p < 0.05$) and decreased LDL-C (−7.9%, $p < 0.05$), TG (−23%, $p < 0.01$), ApoCIII (−11%, $p < 0.01$), ApoB48 (−16.5%, $p < 0.05$) compared to placebo. Fasting plasma glucose (−8.5%, $p < 0.05$), homeostasis model assessment for insulin resistance index ($p < 0.05$) and adiponectin blood concentrations (+23.4%, $p < 0.01$) improved after anthocyanins treatment when compared to control group, as well (Li, Zhang et al., 2015).

Besides lipid-lowering action, the administration of maqui berry extract (486 mg/day) was shown to reduce lipid peroxidation in smokers and overweight subjects (Sahebkar, Serban et al., 2016). This result was confirmed by a further RCT were anthocyanins from maqui berry significantly reduced levels of oxidized LDL, urinary F2-isoprostanes and inflammatory mediators (Davinelli, Bertoglio, Zarrelli, Pina, & Scapagnini, 2015). Epidemiological data suggest that high doses of anthocyanins are also associated with an improvement of PWV and C-IMT (Jennings et al., 2012).

Furthermore, anthocyanins (like many phenols) are the substrate of intestinal metabolism, rapidly biotransformed into phenolic acid derivatives, operated by intestinal microflora. Therefore, the bioavailability of these compounds is variable and the transformation in active or inactive metabolites is also related to intestinal eubiosis conditions. In intestinal dysbiosis conditions, it is possible that the conversion into active metabolites is lower. Anthocyanins are well tolerated without side effects at dosages $\leq$640 mg/day (Marques et al., 2016).

The flavanones of grapefruit juice (340 mL GFJ/day, providing 210 mg naringenin glycosides, or a matched control drink without flavanones for 6 months each, with a 2-month washout between beverages) have shown beneficial effects on vascular function with an improvement in PWV in healthy postmenopausal women ($p = 0.019$) (Habauzit et al., 2015).

In addition, the polyphenol quercetin, a potent anti-oxidant flavonoid found abundantly in onions, has been studied in order to improve cardiovascular health. In particular, a double-blinded, placebo-controlled crossover trial evaluated its antihypertensive and vasorelaxant properties in overweight-to-obese patients with pre-hypertension and stage I hypertension, which received 162 mg/day of quercetin or placebo for 6-week treatment periods separated by a 6-week washout period (Brüll et al., 2015). The results showed that quercetin decreased 24 h systolic BP by −3.6 mmHg ($p = 0.022$) when compared with placebo (mean treatment difference, −3.9 mmHg; $p = 0.049$) in the subgroup of hypertensives. Another trial demonstrated that quercetin reduced systolic blood pressure and plasma oxidized LDL concentrations in overweight subjects with a high-CVD risk phenotype (Egert et al., 2009). Moreover, the intake of quercetin (100 mg/day) for 12 weeks has shown to improve FMD compared with placebo (from 12.5 ± 5.2 to 15.2 ± 6.1; $p = 0.002$) (Choi et al., 2015). Further clinical trials are

suggested to confirm these effects in the long term.

In summary, polyphenols from green tea, cocoa, fruits and onions are able to reduce oxidative stress, improve endothelial function and vascular stiffness. Data on lipid profile are conflicting and should be further investigated.

## 9. Legumes as sources of bioactive peptides

Proteins from soy and lupin have shown preclinical and clinical evidence in the improvement of lipid profile.

In particular, it is possible that their lipid-lowering action is due to the presence of bioactive peptides (such as conglutin-gamma) (Cicero, Fogacci, & Colletti, 2016) and isoflavones (Weggemans & Trautwein, 2003). Nevertheless the cholesterol-lowering mechanisms proposed for soy and lupin are numerous but remain unclear, including the reduction of cholesterol synthesis, the regulation of the expression of the hepatic transcription factor of SREBP-2 (with increased clearance of cholesterol from the blood), the down regulation of SREBP-1 (via PI3K/Akt/GSK3β pathways, with decreased hepatic lipoprotein secretion and cholesterol content), the increase of apolipoprotein B receptor activity or the increase of the faecal excretion of bile salts (Cho, Juillerat, & Lee, 2007; Grieco et al., 2009).

Yellow lupin (*Lupineus luteus*) contains proteins (30–35%), fibers (30%), carbohydrates (3–10%) and fats (6%, of which 81% unsaturated); in addition, there are both macro-elements (as calcium, phosphorus, and magnesium) and microelements (as copper, zinc, chromium and cobalt) (Arnoldi & Greco, 2011). Lupin is a particular legume, because it does not contain phytoestrogens, and it has low sodium content and low glycemic index (Cicero, Fogacci, et al., 2016).

In a randomized, cross over study, 33 hypercholesterolaemic subjects (TC > 6.6 mmol/L) were included and treated for 8 weeks with 25 g/day of lupin protein isolate (LPI) followed by 4 weeks of wash-out and 8 weeks with treatment with active milk proteins (MPI). Compared to baseline, a significant reduction of LDL-C was observed in both groups already after 4 weeks (−12%, $p < 0.008$). In LPI group, the levels of HDL-C increased significantly ($p < 0.036$) and LDL/HDL ratio decreased ($p = 0.003$), compared to MPI group (Bähr, Fechner, Krämer, Kiehntopf, & Jahreis, 2013). These results were confirmed by the same author in a second randomized, controlled, double-blind three-phase crossover trial, including 72 patients with hypercholesterolemia treated for 28 days with LPI, MP (milk protein) or MPA (milk protein +1.6 g/day of arginine). In addition to reducing LDL-C and TC levels (in MPA and LPI groups), LPI group has benefited from an improvement in the levels of homocysteine (compared to MPI and MPA groups), uric acid and triglycerides (Bähr, Fechner, Kiehntopf, & Jahreis, 2015). The cholesterol-lowering properties of lupin were also highlighted in a third RCT with results on the reduction of LDL-C (−12%) comparable to the studies described previously (Fechner, Kiehntopf, & Jahreis, 2014).

Several meta-analyses of RCTs have underlined the cholesterol-lowering properties of soy. In particular, a recent meta-analysis including 35 RCTs and 2670 subjects concluded that soy proteins (in particular β-conglycinin globulin) have a cholesterol-lowering effect with a mean reduction of LDL-C of 3% (−0.12 mmol/L) and triacylglycerols (TAG) of 4% (−0.06 mmol/L) and is able to improve HDL-C of 3% (+0.04 mmol/L), the effect being proportional to the baseline LDL-C level (Tokede, Onabanjo, Yansane, Gaziano, & Djoussé, 2015). The mean tested dose was 30 g/day. Soy proteins are also able to improve non-HDL cholesterol and apolipoprotein B serum levels (Ruscica et al., 2016). This broad effect on several lipid parameters is of particular interest given the attention that the latest guidelines of the European Atherosclerosis Society have towards lipid fraction different from LDL-cholesterol (Catapano et al., 2016).

It is important to highlight that isoflavones do not add significantly to the lipid-lowering effect of soy proteins, but they seem to have direct positive effects on blood pressure levels (Sirtori, Arnoldi, & Cicero, 2015), arterial stiffness (Hazim et al., 2016) and endothelial function (Beavers, Beavers, Miller, Stamey, & Messina, 2012).

In particular, the supplementation in the diet of soybean isoflavones have been suggested to result in arterial vasodilatation, improvement in endothelial function and decreased blood pressure, perhaps by nitric oxide dependent mechanism (Mahn et al., 2005). A meta-analysis of RCTs showed that soy isoflavones had an effect of lowering blood pressure in hypertensive patients, but not in normotensive subjects (Liu et al., 2012). In particular, the subgroup analysis of hypertensive subjects revealed that a greater blood pressure reduction was identified in the soy isoflavone-treated group compared to placebo (5 trials; SBP: −5.94, 95%CI [-10.55, −1.34] mmHg, $p = 0.01$; DBP: −3.35, 95%CI [-6.52, −0.19] mmHg, $p = 0.04$). Moreover, the effects of isoflavone-containing soy-products on vascular health have been evaluated by a meta-analysis of RCTs, which showed that they can modestly, but significantly, improve endothelial function as measured by FMD (Beavers et al., 2012). The overall mean absolute change in FMD (95% Bayesian CI) for isoflavone-containing soy product interventions was 1.15% (−0.52, 2.75); when the effects of separate interventions were considered, the treatment effect for isolated isoflavones was 1.98% (0.07, 3.97) compared to 0.72% (−1.39, 2.90) for isoflavone-containing soy protein.

In summary, the intake of soy and lupin represents a potential adjuvant in the treatment of hypercholesterolemia and to reduce cardiometabolic disease, especially in individuals with moderate to high cholesterol levels. Nevertheless the chronic use of a high quantity of soy products containing isoflavones could interfere with thyroid function and fertility. Furthermore, soybean and its derivatives contain high amounts of phytic acid that reduces the absorption of minerals such as iron, calcium, magnesium, copper, and zinc. The administration of lupin is safe and well tolerated, without severe side effects, mostly of gastrointestinal nature. Nevertheless the high doses of these vegetable proteins are required to obtain a significant reduction of LDL-C in some cases could reduce patient compliance, particularly in the long-term and should be associated by a careful balance of protein from other dietary sources.

## 10. Conclusion

Despite the availability of a large number of trials demonstrating positive short-term effects of several food and plant bioactives on major cardiovascular risk factors (hypercholesterolemia, hypertension, type 2 diabetes), only a few of them have also demonstrated a direct positive effect in prevention of vascular aging. In particular, promising data are available as it regards green tea extract, red yeast rice (alone or associated to berberine or antioxidants), soy (protein + isoflavones) and lupin, omega-3 polyunsaturated fatty acids (EPA and DHA), curcumin, and vitamin E. Supplementation with red yeast rice and omega-3 polyunsaturated fatty acids has been associated with a decrease in cardiovascular mortality risk in selected subcategories of high-risk patients. Encouraging results have also been obtained from cocoa polyphenols, which have been shown to have significant benefits in cardiovascular prevention, modulating blood pressure, endothelial function and improve vascular stiffness. For this reason, the COSMOS American study (ongoing) will be helpful to understand the long-term relationship between supplementation of cocoa polyphenols (600 mg/day), cardiovascular events and

cardiovascular mortality in about 18,000 adults (compared to placebo).

Future clinical research will have to focus more on middle term modification of instrumental markers of vascular aging than on short-term effects on indirect laboratory risk markers. Of course, long-term trials on CVD mortality risk will manage to furnish a definitive indication for the preventive use of a specific food and plant bioactive as a preventive agent.

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