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Combinations of phytomedicines with different lipid lowering activity for dyslipidemia management: The available clinical data

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ABSTRACT

Background: Cardiovascular diseases are the primary cause of death and the leading cause of disability in industrialized countries. Dyslipidemia is a major independent and reversible risk factor for these diseases: it is estimated that a reduction of 1 mmol/l (38 mg/dl) of LDL cholesterol is associated with a risk of developing a cardiovascular complication reduced by 25%, a reduction potentially achieved by life-style improvement associated to adequate dietary supplementation with bioactive substances.
Aim: The aim of this review is to focus on the major phytochemical nutraceuticals combinations supported by clinical trials that have demonstrated positive effects in the treatment of dyslipidemia.
Main text: There are many nutraceuticals with significant lipid-lowering properties: most of them are used in association with a low dosage, because that permits to reduce the risk of side effects and theoretically to improve efficacy. In fact, natural products with different synergetic lipid-lowering could be combined: they can reduce the absorption of lipids from the bowel and/or increase their excretion (soluble fibers, plant sterols, probiotics), enhance the hepatic uptake of cholesterol (berberine, soybean proteins), inhibit Hydroxy-Methil-Gglutaryl Coenzyme A reductase enzyme and consequently the hepatic synthesis of cholesterol (monacolins, policosanols, allicin, soybean proteins, bergamot); furthermore some products are able to reduce the oxidation of the LDL and increase the thermogenesis and lipid metabolism (chlorogenic acid).
Conclusion: Rational combinations of nutraceuticals with different lipid-lowering activities, whether associated with an appropriate lifestyle, should provide an alternative to drug treatment in patients in primary cardiovascular disease prevention with mildly added cardiovascular risk and in some statin-intolerant patients.

Introduction

Dyslipidemia is a well-established modifiable cardiovascular risk factor and its treatment is an essential aim in preventing cardiovascular diseases, which represent the leading cause of death and disability in industrialized countries (Baigent et al. 2005; Schnabel et al. 2015).

Current guidelines highlight lifestyle intervention as a primary issue in the treatment of patients with hypercholesterolemia, but it is often insufficient to adequately control the lipid pattern (ACC/AHA 2013). On the other hand, the use of drugs, in particular statins, implies the risk of several side effects, whit a somewhat doubtful risk-efficacy ratio in patients with low-added cardiovascular risk (Arca and Pigna 2011). The increasing need to find a non-pharmacological alternative, in particular for patients with moderate hypercholesterolemia, low cardiovascular risk or intolerant to traditional pharmacological treatment, has led to clinically test many phytochemical nutraceuticals that have shown lipid-lowering properties (Cicero et al. 2015a). Nutraceuticals are devices between nutrients and drugs, which can give a supplementation of nutrients with beneficial effects on health (Kalra 2003): there have been studied over 40 lipid-lowering phytochemical nutraceuticals which have demonstrated their benefits on lipid metabolism and on surrogate markers of cardiovascular health, and the results of preclinical and clinical trials sustain the use of these substances in every day management of dyslipidemias (Mannarino et al. 2014). In recent years, the most of lipid-lowering nutraceuticals is commercialized as an association of two or more components: this permit lower dosages of single elements and to reduce the risk of side effects (Cicero et al. 2015a). Furthermore, it allows a synergetic effect of the substances, that act with different mechanisms of action on lipid metabolism: in fact some of them can reduce the absorption of lipids and biliary salts by the bowel (soluble fibers, glucomannan, plant sterols), while other enhance the

Abbreviations: HDL-C, high density lipoprotein cholesterol; HMGCoA, hydroxy-methil-glutaryl coenzyme A; LDL-C, low density lipoprotein cholesterol; MDA, malon-dialdehyde; PCSK9, proprotein convertase subtilisin/kexin type 9; TC, total cholesterol; TG, triglycerides.

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hepatic uptake of cholesterol (berberine, soybean proteins), some are able to induce LDL-C excretion (berberine, soy proteins, chlorogenic acid), while others inhibit Hydroxy-Methil-Glutaryl Coenzyme A (HMGCoA) reductase enzyme limiting the hepatic synthesis of cholesterol (monacolins, policosanols, allicin from garlic, bergamot); furthermore some nutraceuticals are able to reduce the oxidation of the LDL (chlorogenic acid) and increase the thermogenesis and lipid metabolism (green coffee) (Cicero et al. 2012).

The aim of this review is to focus on the major phytochemical nutraceuticals combinations supported by clinical trials that have demonstrated positive effects in the treatment of dyslipidemia.

Data selection

A systematic search strategy was developed to identify trials in both MEDLINE (National Library of Medicine, Bethesda, MD; January 1965 to July 2015) and the Cochrane Register of Controlled Trials (The Cochrane Collaboration, Oxford, UK). The terms 'nutraceuticals', 'dietary supplements', 'herbal drug', 'phytochemicals', 'hypercholesterolemia', 'functional food', 'dyslipidemia' and 'combination nutraceuticals' 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. They subsequently reviewed the potential trials to determine their eligibility. They selected papers reporting recent comprehensive reviews or meta-analyses, or original clinical trials on the combination of phytochemical compounds with demonstrate lipid-lowering action.

Red yeast rice and berberine

The most studied combination of lipid lowering-nutraceuticals is a property product containing a red yeast rice extract with 3 mg monacolin K and berberine 500 mg per daily dose (Armolipid Plus®).

Red yeast rice extract (*Monascus purpureus*) contains monacolins that compete structurally at HMGCoA reductase level with HMGCoA, precursor of mevalonate, thus reducing plasma cholesterol (Heber et al. 1999). After the positive results reported in literature, the European Food Safety Authority (EFSA) recognized that there is a cause-and-effect relationship between the consumption of monacolin K from red yeast rice and the maintenance of normal blood LDL-C concentrations [EFSA (2011)].

Berberine is a natural plant extract from *Berberis aristata* bark, that reduces cholesterolemia by increasing LDL-Cholesterol receptor on the liver cell surface and inhibiting TG biosynthesis via the inhibition of Proprotein convertase subtilisin/kexin type 9 (PCSK9) and the activation of 5'AMP activated proteokinase (Brusq et al. 2006; Cicero and Ertek 2009).

So, it was supposed and tested that the combination of these natural products could have an additive or synergistic lipid-lowering effect in humans. After a preliminary trial (Cicero et al. 2007), many others confirmed this hypothesis was true.

Among others, in a large study carried out in the setting of every day clinical practice on dyslipidemic patients the use of the tested association was associated to a persistent and significant improvement of different lipid parameters with a reduction of −19.1% for TC ($p < 0.001$), −23.5% for LDL-C ($p < 0.001$), + 11.6% for HDL-C ($p < 0.001$), −17.9% for TG ($p < 0.001$) after 16 weeks (Trimarco et al. 2011).

In another 8-week randomized, double-blind cross-over clinical trial, carried out in the setting of a lipid clinic, the same combination was able to increase HDL-cholesterol (4.8%) and to reduce TC (−12.8%) and LDL-C (−21.1%) in patients with moderate dyslipidemia and metabolic syndrome with results similar to pravastatin (−16% and −22.6%, respectively) (Ruscica et al. 2014).

The treatment is usually well-tolerated, even when employed by elderly hypercholesterolemic patients who were previously statin-intolerant (Marazzi et al. 2011).

As surrogated markers of cardiovascular health, the red yeast rice-berberine association has also shown to improve endothelial function (Affuso et al. 2010) and pulse wave velocity (Cicero et al. 2013) in dyslipidaemic patients.

Red yeast rice and policosanols

Red yeast rice has also frequently associated to policosanols, also mildly inhibiting the HMGCoA reductase (Cicero and Ertek 2009).

A brand dietary supplement made of *Monascus purpureus* titrated extract and octacosanols, also containing a low niacin dose, was tested 111 Caucasian patients with low cardiovascular disease risk (<20% by Framingham algorithms), comparing them with the anti-hypercholesterolemic effect of a low dosage of Pravastatin on 20 subjects with similar risk profile. In this study, the tested dietary supplement determined a significant decrease of TC and LDL-C, and TG in moderately hypercholesterolemic subjects without clinically relevant change in liver and muscular toxicity markers. The reduction of LDL-C reached the 20%, and it is similar to that obtained with a well-known effective statin like Pravastatin (Cicero et al. 2005).

These effects were confirmed in the setting of a lipid clinic where the tested association induced after 4 months a significant reduction in TC (−21.3%), LDL-C (−29%), and non-HDLC (−26%) ($P < \text{or} = 0.001$) (Stefanutti et al. 2009).

Dietary supplements containing red yeast rice extract and policosanols has also been successfully employed in hypercholesterolemic children (Guardamagna et al. 2011)

Red yeast rice and n-3 polyunsaturated fatty acids

After the positive results reported in literature, the European Food Safety Authority (EFSA) recognized that there is a cause-and-effect relationship between the consumption of omega-3 polyunsaturated fatty acid intake and normal cardiac function (EFSA 2010).

A clinical trial evaluated the effects of their association for 8 weeks in subjects affected by primary polygenic hypercholesterolemia and metabolic syndrome, pharmacologically untreated: the results showed a significant decrease in TC (−42.50 ± 18.1 mg/dl; −16% ± 2%), LDL-C (−37.6 ± 13.6 mg/dl; −22 ± 3%), TG (−19.8 ± 25.1 mg/dl; −9 ± 5%), and non-HDL-C (−43.1 ± 17.7 mg/dl; −21 ± 3%) and a significant increase in HDL-C (+ 1.5 ± 0.5%) (all $p < 0.001$), without the modification of safety parameters.

In particular, 75% of subjects reached an LDL-C target of less than 160 mg/dl and 25% of less than 130 mg/dl. Furthermore, the study highlighted a greater decrease in TG levels only in subjects with baseline TG > 50 mg/dl, who reached a 11% reduction ($p < 0.001$ vs. subjects with baseline TG < 150 mg/dl) (Cicero et al. 2015c).

Red yeast rice and plant sterols

Plant sterols (phytosterols') and stanols (saturated form of sterols) are natural constituents of plants, structurally related to cholesterol, which are abundant in vegetable oils and olive oil, but also in fruits and nuts: they reduce cholesterol absorption in the intestinal gut, possibly by competitively inhibiting its incorporation into the mixed micelles in the small intestine, thereby reducing plasma LDL-C concentrations (Badimon et al. 2010). Combinations of plant sterols/stanols with other lipid-lowering ingredients have shown to potentate their cholesterol-lowering effects and, in some cases, add triacylglycerol-lowering effects (Kamal-Eldi and Moazzami 2009).

The association of red yeast rice and plant sterols mime in some way the one of statins and ezetimibe. A product combining red yeast rice and phytosterols has been demonstrated to improve cholesterol