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Nutraceuticals and cholesterol-lowering action

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ABSTRACT

Nutraceuticals play an important role in cardiovascular prevention in patients with dyslipidemia. Many scientific studies support the use of these substances alone or associated with other drugs in clinical practice. Specifically, monacolines, berberine, policosanol and gamma-oryzanol could significantly reduce cholesterolemia. However, there is still an insufficient number of studies demonstrating morbidity and mortality outcomes of nutraceuticals, nor are sufficient data regarding the use of nutraceuticals in different types of patients, on tolerability, safety, target population, modality and duration of use present in the literature.

1. Introduction

Cardiovascular diseases are the leading cause of mortality and morbidity in the world: prevention of these diseases has therefore assumed a relevant role in clinical practice. The LDL blood cholesterol is the most known risk factor, so relevant that approximately 25% of the adult population has abnormal levels. Cardiovascular disease risk is proportional to blood cholesterol LDL levels, even in the range of values "high-normal" (i.e. LDL-C between 130 and 160 mg/dL) [1,2].

Nutrients play an important role in maintaining the organism's homeostasis to the dose taken with food, but some of them may have specific active effects if supplemented with higher dosages.

The term nutraceutical means a natural substance derived from food sources which, when taken alone or in concentrated form, has well-known pharmacological properties. From an institutional point of view, the only official definition of "nutraceutical" is that of the Canadian Pharmacopoeia which defines it as an isolated or purified food product which is generally sold in the form of pharmaceutical drug not associated with food, and which must have proven physiological benefits or provides protection against chronic disease.

In order to be defined efficiently, nutraceuticals must have a pharmacological effectiveness that exceeds the spontaneous variance of the parameter to be modified.

However, they must not be too effective so as not to be equated to drugs, which is precisely why industries are not interested to invest in primary outcome research (morbidity and mortality), but only in secondary outcomes or derivatives [3].

Among cholesterol-lowering action nutraceuticals, the most studied are monacolin of fermented red rice, polycosanol and berberine.

Other substances have a less evident action (e.g. the active principles of plants with cholagogue–choleretic action such as artichokes) or have a good potential but have not yet adequately investigated (e.g. bergamot polyphenols, krill oil). The most efficient nutraceuticals act on the liver which impacts the lipid metabolism, particularly the LDL cholesterol metabolism. Fibers and phytosterols, instead, taking action on the intestinal absorption of cholesterol, appear to be of less impact on the control of cholesterol blood levels [4].

2. Monacolin

Monacolins are fungal metabolites isolated from *Monascus purpureus* cultures, a contaminant responsible for the reddish color of rice upon which they grow (so-called "fermented red rice"). There are several kinds of monacolins; they have a complex molecular structure which is very similar to that of natural statins, in particular to lovastatin. Their metabolism is similar to that of the fat-soluble statins, which are quite easily absorbed by the intestine as well as metabolized by the isoform 3A4 cytochrome P450 [5].

Like statins, monacolin functions through the reversible inhibition of the hepatic enzyme which limits cholesterol synthesis, the 3-hydroxy-3metil-glutarilCoenzimaA reductase. The cholesterol-lowering effect of monacolin has been studied in a series of patient categories: hypercholesterolemic, renal failure, HIV in highly-effective antiretroviral therapy, post-infarction, and the elderly. In Italy a 3 mg dose of monacolin extract is in use, with the limitation that the evaluating HPLC is able to recognize and dose only a few types.

The administration of monacolin 3 mg/day obtains a maximum reduction of 10–15% LDL cholesterol.

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By administering a 10 mg dose, recently defined as effective in reducing blood cholesterol by the European Food Safety Authority (EFSA), the percentage may reach 20%.

In addition, monacolins, like statins, have a role in the reduction of high-sensitivity C-reactive proteins and improvement in flow-mediated dilation of the blood vessels. A clinical trial of secondary prevention intervention conducted in China (Fig. 1) on a population of 4780 patients with coronary heart disease, of which 1445 over the age of 65, with follow-up of 7 years, gave surprising results in terms of reducing the risk of lethal and non-lethal recurrent events, probably compromised by the lack of other active interventions on patients considered [6].

Although some studies have shown good tolerability of monacolins by patients who are intolerant to statins [7], particular caution should be used when treating patients with myopathies who take drugs metabolized by cytochrome P450, especially those with a narrow therapeutic range, such as cyclosporine. The low dosages used in Italy should not create problems in patients with renal or liver diseases.

3. Berberine

Berberine is a highly concentrated natural alkaloid found in numerous medicinal plants (*Hydrastis canadensis*, *Coptis chinensis*, *Berberis aquifolium*, *Berberis vulgaris*, *Berberis aristata*). Its oral bioavailability is low. The substance is metabolized by the liver and excreted primarily via the bile after glucuronidation. The target organ is mainly the liver, with a complex mechanism of action on all the metabolic structures, which is still not fully understood (Fig. 2) [8].

Berberine probably inhibits the transcription of the mRNA encoding the proprotein convertase subtilisin/kexina type 9 (PCSK9), which is the protein that facilitates the separation of the hepatic LDL receptor from the cell surface towards the lysosomes where it is usually degraded with a resulting prolongation of the receptor's half-life, which can then recapture more LDL cholesterol from the bloodstream to be sent for disposal via the bile.

Berberine effects are clearly not dose-dependent: already 500 mg/day achieves a reduction of approximately 20% of the LDL cholesterol and 25% of triglycerides in pure hypercholesterolemics, in mixed dyslipidemics, in type 2 diabetics and in hepatopathics [9]; its action on insulin resistance in type 2 diabetics, is comparable to that obtained with the full dose of metformin, which also shares the same gastrointestinal side effects [10].

Although there is a lack of important studies on the clinical outcomes of this substance, preliminary data show how it is able to increase the number of circulating endothelial progenitor cells (direct laboratory marker in vascular rejuvenation), reduce the number of circulating endothelial microparticles (laboratory marker of endothelial dysfunction) and, finally, improve flow-mediated vasodilatation (instrumental marker of endothelial function) [11]. However, berberine may interfere with the metabolism of cyclosporine, but tolerability is generally high.

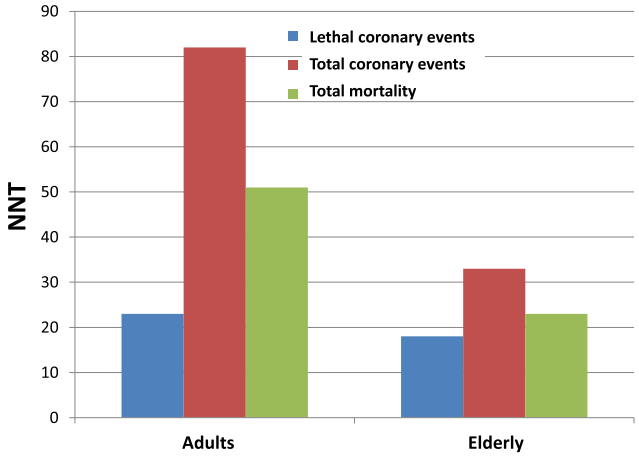

Fig. 1. Number needed to treat (NNT) a subjects in order to avoid a lethal coronary event, a coronary event (any) or a death for any causes in adults and elderly in secundar prevention treated with red yeast rice.

4. Polycosanols

Polycosanols are a mixture of primary aliphatic saturated alcohols of variable length, drawn from the wax of sugar cane, but also from beeswax, rice bran and other plants. The main components of the mixture are octacosanols (ca. 60%), triacontanols (ca. 10%), esacosanols (approx. 6%), and other eptacontanols.

Polycosanols act through the inhibition of mRNA coding synthesis for 3-hydroxy-3-methyl-glutarilCoenzyme A reductase [12]. The response to these nutraceuticals is extremely variable because their activity depends greatly on the polyalcohols prevailing in the mixture administered. There are many clinical trials of a single Cuban research center supporting the cholesterol lowering efficacy of such molecules which would be able to determine a decrease in LDL of up to 20% at a dosage of 10 mg/day. However, more recent studies conducted on different populations in Western Europe, patients with more severe pathologies and probably different extracts of polycosanol, tend to question their effective lipid-lowering ability. Tolerability seems good in the short to medium terms [13].

5. Other active substances

The active ingredients of most herbal medicines for the reduction of cholesterol (e.g., *Allium sativum*, *Cynara scolimus*, *Sylibum marianum*) related to lipid-lowering (usually mild) are not known or are attributed to the effectiveness of the plant complex.

Gamma-oryzanol extracted from rice bran seems to exert its mild cholesterol-lowering action through a 4-component desmetil sterolica interfering with the intestinal absorption of dietetic cholesterol [14,15]. Bergamot-derived polyphenolic fraction seems to have a mild but significant cholesterol-lowering effect, accompanied by reductions of malondialdehyde, oxyLDL receptor LOX-1 and phosphoPKB, which are all biomarkers of oxidative vascular damage, in peripheral polymorphonuclear cells [16].

The action mechanism is interesting, but there is still a great lack of evidence of the cholesterol-lowering efficacy in humans. High doses (grams) of polyunsaturated fatty acids omega 3 and nicotinic acid mostly reduce triglycerides, while the levo-carnitine only reduces lipoprotein (a).

6. Assembled products

In Italy the majority of nutraceuticals with lipid-lowering action is commercially available in the form of composite, or association of different substances at reduced dosage, assembled so as to exploit the presumed synergy of the components.

There are various reasons why it might be preferable to commercialize products of this kind: a) legal restrictions (e.g. you cannot use more than 10 mg of monacolins/dose by law), b) side effects (e.g., doses of berberine exceeding than 500 mg/day are more likely to cause gastrointestinal problems), and c) economic reasons (a more complex formulation allows competitive differentiation and a possible saving on raw material).

Sometimes this phenomenon leads to the creation of products where there is no real rational association and the active substances are under-dosed in relation to the lipid-lowering effect sought.

Therefore, before prescribing these nutraceuticals, it would be desirable to investigate the reliability of the origins of the raw materials, dosage compatibility of the individual components with the desired effectiveness, the rationality of the synergy in relation to the action mechanism of the various formulations of substances, and the existence of studies to confirm the effectiveness of the association.

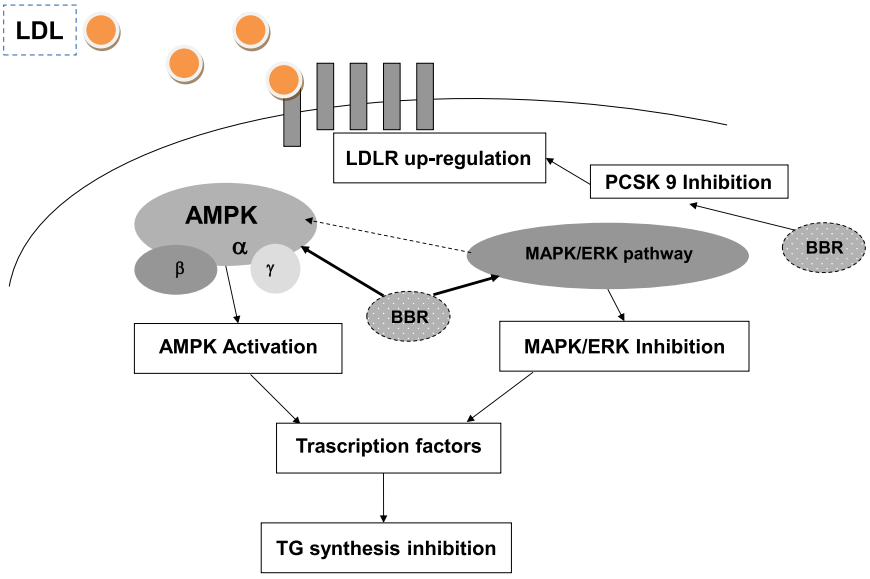

Fig. 2. Lipid-lowering mechanism of action of berberine.

One of the most tested associations is between monacolins (3 mg) and polycosanol (10 mg), which has the rationale of combining an inhibitor of the synthesis of the hydroxymethyl-glutaryl-coenzyme A reductase (polycosanol) with an inhibitor of the activity (monacolin). This association would apparently produce a reduction of LDL cholesterol of about 15% [17,18].

Another preconceived association with a rational formulation combines berberine with cholesterol synthesis inhibitors which facilitates the disposal of circulating cholesterol (Fig. 3). This kind of addition increases the cholesterol-lowering efficacy (up to 25% reduction of LDL cholesterol), also acting on triglycerides (−20%). Furthermore, it has the advantage of having been proved effective in statin-intolerant patients [19] and to have positive effects on indirect markers of vascular health such as the flow-mediated vasodilation and the carotid–femoral pulse wave velocity [20].

7. Conclusions

The use of substances derived from nutrients for lipid-lowering purposes represents a viable alternative to conventional therapy which for ethical and economic reasons cannot be administered to such a large population affected by alterations in lipid metabolism, in the absence of an elevated cardiovascular risk. However, in the face of a substantial number of nutraceuticals with known efficacy and safety on in vivo and ex vivo models, only few substances have been adequately studied in humans, especially in patients who are particularly vulnerable such as pregnant women, the elderly, and patients with liver disease or renal failure [21].

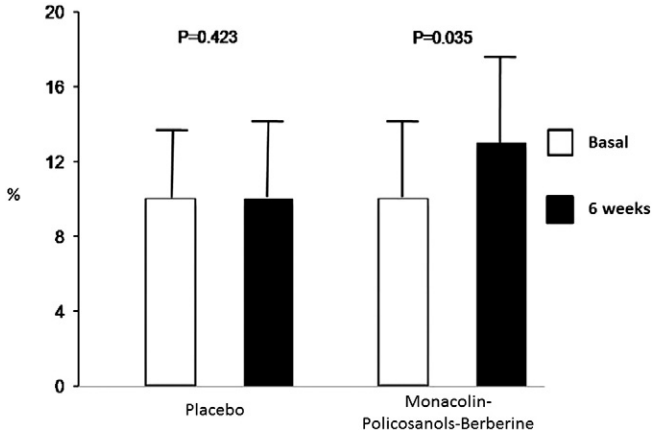

Fig. 3. Changes in flow-mediated dilation after treatment with placebo or lipid-lowering combined nutraceuticals.

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