

Role of nutraceuticals in hypolipemic therapy

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Nutraceuticals is an area of pharmacology regarding food components or active ingredients in food that may be used as therapeutic agents. This includes a large number of compounds, such as an active ingredient, food supplements (i.e., supplements the normal diet), and functional foods (i.e., foods enriched with components with specific therapeutic or protective functions), as well as preparations based on medicinal herbs. Most compounds are vegetable originated, but there are also substances with animal origin (e.g., fish oil). Recent studies have shown promising results for these drugs in various pathological complications such as diabetes, atherosclerosis, cardiovascular diseases, cancer, and neurological disorders. These conditions involve many changes, including alterations redox state, and most of nutraceuticals have antioxidant activity with the ability to counteract this situation. Hence, nutraceuticals are considered as sources of health promotion, and they, nowadays, have received a considerable interest. A market research recently proposed that the worldwide nutraceuticals market is expanding and would reach US \$250 billion by 2018. Since nutraceuticals are generally considered like "foods," their use does not strictly follow the same rules of classical drugs and have patent protection. Thus, a large

amount of preparations have been suggested to have a therapeutic effect and are rapidly available for patients.^{1,2}

There are a variety of nutraceuticals with a potential lipid-lowering effect, and therefore useful in the cardiovascular prevention. Nevertheless, in relation to the scarcity of experimental studies, these molecules do not always have solid scientific evidence with regard to both mechanisms of action and clinical efficacy. Data produced by small studies were often disavowed by larger and controlled studies or meta-analytic data. Some nutraceuticals are also able to enhance the action of the classic drugs (including statins), due to different mechanisms of action.

Policosanols³

These are a mixture of natural long chain aliphatic alcohols obtained from a wide variety of plants. It has been suggested that policosanols might inhibit the activity of HMG-CoA reductase, but this is not definitively confirmed. In the early 90s, a number of clinical studies suggested a lipid-lowering effect of policosanols in different types of patients (healthy volunteers, hypercholesterolemics, diabetics, or postmenopausal women), with reduction in LDL-cholesterol similar to that of statins (about 25%), and a 10% increase of HDL-C. Some reports suggested benefits even on clinical outcomes, including coronary ischemia or claudication; these treatments appeared also very well tolerated by patients.

Polyphenols⁴

This is a very large family of substances available in the plant world. The main feature is the presence of multiple phenolic groups having a potent anti-oxidant effect; for this reason polyphenols present in some foods typical of the Mediterranean diet (olive oil, red wine, fruits, vegetables) are considered to account for the protective effect of this nutritional model; drug preparations, may be for a different bioavailability, do not seem to have the same clinical effect.

Garlic⁵

Allicin, a substance contained in the bulb of garlic, seems to be able to reduce both synthesis (perhaps through the inactivation of HMG-CoA reductase) and intestinal absorption of cholesterol, and therefore to have lipid-lowering properties, with reductions of total cholesterol reported between 9 and 12%. These data have recently been substantially refuted by Gardner and colleagues: these authors, in a randomized placebo-controlled trial, have not documented any cholesterol-lowering effect with different formulations of garlic.

Probiotics⁶

They have received a lot of attention due to the potential benefits that they seem to have in different fields. Regarding lipid metabolism, probiotics could lower cholesterol absorption through direct cellular effects or mediated by bile metabolism. Several studies on different patients have documented significant reductions in total cholesterol, up to 40%. However, exact mechanisms of action were not identified, and

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those proposed (such as the inhibition of intestinal absorption of cholesterol) are usually dependent on bacterial strains and methods of execution of experiments, often very different from the "in vivo" conditions. More recently, it has been postulated a role of expression of the gene of bile salt hydrolase activity in the lactobacilli strains to explain the cholesterol-lowering action, even this hypothesis itself does not seem completely convincing **Guggul⁷**

This is a resin extracted from the bark of *Commiphora mukul*, a small thorny tree, also known as the tree of myth, used medically in India for hundreds of years. The active components, guggulsterone E and Z, have been demonstrated to have an antagonistic action of FXR, a nuclear receptor involved in the bile metabolism. Based on this data, published in *Science* in 2002, and given the close relationship between cholesterol and bile metabolisms, it has been also proposed a role in modulating plasma lipid levels.

Plant Sterols⁸

Plant sterols decrease intestinal absorption of cholesterol through the reduction of the content of cholesterol within the micelles and a consequent lower proportion of absorbable cholesterol. In addition, some studies suggest that phytosterols are able to compete with cholesterol in the carrier of the intracellular incorporation (NPC1L1), and also increase the activity of transmembrane proteins responsible for the excretion of cholesterol (ABCA1) and plant sterols (ABCG5 and ABCG8) in the intestine and liver, with the net effect of increasing the release of both sterols into the intestinal lumen by enterocytes and in the bile ducts in the liver. The lower intestinal absorption of cholesterol induced by plant sterols decreases

cholesterol pool of liver, which responds by increasing the expression of LDL receptors, finally resulting in higher uptake of plasma LDL and therefore in a net hypocholesterolemic effect. **Fermented Red Rice⁹**

The fermentation of red rice by a fungus (*Monascus purpureus*) produces a substance called monacolin K, which inhibits the synthesis of cholesterol. The monacolin K is also known as lovastatin, a statin available in the market worldwide. The red yeast rice also produces other monacolins that may enhance the inhibition of HMG-CoA reductase. In addition, recent data show that, compared to the classical lovastatin, monacolin K extracted from red yeast rice have even a higher bioavailability with a higher efficacy at the same dosage. **Berberine¹⁰**

This substance, with a bitter taste and intense yellow color, is present in the bark, roots and stems, including underground (rhizome) of plants of the genus *Berberis*, such as barberry (*Berberis vulgaris* L.). For the antimicrobial and antisecretive properties, berberin is traditionally used in the treatment of infections. In recent years, most attentions have been on the metabolic properties of berberine. In 2004, Kong et al., have shown that berberine reduced plasma cholesterol by 29%, triglycerides by 35%, and LDL cholesterol by 25%, whereas it did not modify HDL-cholesterol levels. Berberine increases the number of LDL receptors on the hepatic cell surface, similarly to statins. However, during statin therapy, the exposure of LDL-receptors on cell membranes follows the decrease of the endogenous cholesterol synthesis and the subsequent reduction of intracellular cholesterol pool, whereas the action of berberine

seems linked to the ability to inhibit a protein (PCSK9) responsible for the partial degradation of LDL receptors in the liver. For these reasons, berberine may have synergistic effects with statins. It is relevant to remember that inhibition of PCSK9 by monoclonal antibodies is a new lipid-lowering strategy and several clinical trials are currently in progress

In conclusion, nutraceuticals represent a valid alternative hypolipidemic treatment, and thus have a role in cardiovascular prevention strategies. Nutraceuticals have multiple physiological benefits and their use may be a valid alternative or complementary therapy to conventional treatment in many fields. A proper and reasoned use may help to prevent chronic diseases, increase life expectancy, support the structure or function of the body, delay the aging process, and help maintain overall good health. Due to the growing industrial and commercial interest in the future, it is desirable to have better regulations and improve the scientific agreement to warrant safe usage and clinical effectiveness.

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