European Journal of Internal Medicine 25 (2014) 592–599

Contents lists available at ScienceDirect

European Journal of Internal Medicine

journal homepage: www.elsevier.com/locate/ejim

Review Article

Nutraceuticals for the treatment of hypercholesterolemia

Massimo R. Mannarino *, Stefano Ministrini, Matteo Pirro

Unit of Internal Medicine, Angiology and Arteriosclerosis Diseases, Department of Medicine, University of Perugia, Perugia, Italy

ARTICLE INFO

Article history:
Received 13 December 2013
Received in revised form 7 April 2014
Accepted 10 June 2014
Available online 2 July 2014

Keywords:
Nutraceuticals
Hypercholesterolemia
Red yeast rice
Phytosterols
Berberine

ABSTRACT

Hypercholesterolemia is a well-established modifiable cardiovascular risk factor and its treatment is an essential aim in preventing cardiovascular disease. Current guidelines highlight lifestyle intervention as a primary issue in the treatment of the patient with hypercholesterolemia. Therapeutic lifestyle changes are often insufficient to achieve desirable cholesterol levels. This is particularly true for high risk patients; however, also low risk patients, whose cholesterol levels are not necessarily far from recommended targets, have either sub-optimal or even significantly increased lipid levels. Nutraceuticals are borderline devices between nutrients and drugs providing a supplementation of particular nutrients with beneficial effects on health. Several nutraceuticals have been suggested to improve plasma lipid profile. The literature counted over 40 nutraceutical substances with a supposed beneficial effect on lipid metabolism; for some of them a number of clinical trials highlighted a cholesterol lowering effect and a possible positive influence on cardiovascular prognosis.
The aim of this article is to review the main evidences supporting or denying the efficacy and safety of some of the most commonly used nutraceuticals with supposed cholesterol lowering activity.

1. Introduction

Cardiovascular disease (CVD) is the foremost cause of death and disability in the Western countries [1]. Hypercholesterolemia is a well-established modifiable cardiovascular risk factor and its treatment is pivotal in preventing CVD. A meta-analysis by Baigent et al. estimated that every 1.0 mmol/L (38.67 mg/dL) low density lipoprotein cholesterol (LDL-C) reduction is associated with a corresponding 22% reduction in CVD morbidity and mortality [2].

Although the latest AHA/ACC Guidelines on the Treatment of Blood Cholesterol suggested to abandon the use of risk based cholesterol targets [3], we have learned from clinical trials and outstanding guidelines that optimal fasting cholesterol levels change accordingly to the theoretical cardiovascular risk of each individual [4]; thus, even average cholesterol levels, when associated with other risk factors, may significantly increase CVD risk [5].

Low risk patients usually have fasting cholesterol levels slightly above the recommended therapeutic target. In a population of dyslipidemic outpatients, the average distance to the therapeutic goal of patients at low cardiovascular risk was about 20 mg/dL [6]. This notwithstanding, most of the low risk individuals presenting non-optimal levels of fasting cholesterol are undertreated or not treated at all. The National Health and Nutrition Survey (NHANES) revealed that among adults treated for cardiovascular prevention, hypercholesterolemia is the most common risk factor treated in a sub-optimal way [7].

Several reasons might suggest why this group of patients is so poorly treated. Cholesterol targets are frequently underrated by health care professionals, drug uptitration is rarely performed, patient's compliance to drug prescription is limited, and drug intolerance and side effects are not uncommon; accordingly, a number of patients do not tolerate statins because of myalgias, muscular or liver toxicity [8,9]. The limited burden of CV risk of low risk patients with sub-optimal cholesterol levels and the possible occurrence of adverse reactions, make treatment of low risk patients with statins a matter of intense debate [10,11].

Current guidelines highlight the key role of lifestyle intervention in the treatment of patients with increased cholesterol levels [3]. This is particularly true in patients whose therapeutic targets are reachable with non-pharmacological measures. Reduction in the amount of nutrients which negatively affect lipid profile is the cornerstone of diet modification: total fat intake should not exceed 35% of total caloric intake [12]; intake of saturated fatty acids (SFAs) should be reduced below 6% of total caloric intake and trans-saturated fatty acids below 1%; dietary cholesterol intake <200 mg/day is still far to be accepted as a strong recommendation [3].

Also consumption of foods which favorably affect lipid metabolism should be encouraged. A number of dietary components are supposed to improve cholesterol metabolism. These nutrients may be naturally taken with the diet by increasing the consumption of foods such as fish, nuts, vegetables and fruits. To achieve a "therapeutic" intake of healthy nutrients, it could be useful to supplement our diet with either artificially enriched foods or nutraceuticals; indeed a common diet contains only a modest amount of these nutrients.

* Corresponding author at: Unit of Internal Medicine, Angiology and Arteriosclerosis Diseases, University of Perugia, Hospital "Santa Maria della Misericordia", Piazzale Menghini, 1-06129, Perugia, Italy. Tel.: +39 075 5783172; fax: +39 075 5784022.
E-mail address: massimo.mannarino@unipg.it (M.R. Mannarino).

http://dx.doi.org/10.1016/j.ejim.2014.06.008
0953-6205/

The term nutraceuticals is a chimerical word, resulting from the fusion of "nutrition" and "pharmaceutical"; it was first formulated by Stephen Defelice in 1989 and according to his definition "nutraceuticals are food or part of a food that provides medical or health benefits including the prevention and/or treatment of a disease" [13].

According to the Food and Drugs Administration (FDA) a "dietary supplement" is a product intended to supplement one or more nutrients, with the intent of increasing their total daily intake [14]. A "functional food" is instead defined as a food product to be taken as a part of the usual diet in order to have beneficial effects that go beyond basic nutritional function. Functional foods can be enriched with ingredients that usually are not present in that particular food, or contain an amount of a specific nutrient larger than usual. FDA regulates dietary supplements to ensure their safety, wholesomeness and their labeling to be truthful and not misleading [15].

Similarly, the European Commission regulates the nutraceutical market through the European Food Safety Authority (EFSA), which authorizes the labeling of food products with health claims. Basically a health claim must be based on accepted scientific evidences, which demonstrate a significant effect in humans and a cause-and-effect relationship between the consumption of the food and claimed effect on humans. Producers must declare the target population for the intended health claim and the recommended quantity of nutrient, necessary to obtain the claimed beneficial effect; they must declare if there are categories of persons who should avoid using the nutrient [16].

Official position statements and qualified opinions expressed by EFSA and FDA about the main nutraceuticals used for the treatment of hypercholesterolemia are summarized in Table 1.

2. Role of nutraceuticals in the treatment of hypercholesterolemia

The literature counted over 40 nutraceuticals with a supposed beneficial effect on lipid metabolism [17]. Some of these substances have proven efficacy in reducing both serum lipids and CV risk; in addition, some of them have been demonstrated to affect beneficially surrogate markers of vascular damage, such as arterial intima-media thickness (IMT), endothelial dysfunction and arterial stiffness [18].

However many trials investigating the effect of nutraceuticals on lipid metabolism have important methodological drawbacks in terms of study design, population characterization and outcome selection. We tried to select and display the results that appeared, in our opinion, most reliable; the results that we present are not intended as guidelines for clinical practice and this article has to be intended rather as an informative paper.

In Table 2, cholesterol-lowering efficacy of some of the most commonly used nutraceuticals is reported.

2.1. Soy derivates

Soybeans contain substances which could have a positive effect in reducing cardiovascular risk. Soy protein and isoflavones have been intensively studied in the last 30 years because they are supposed to be responsible of the main beneficial effects of the soy products.

Major isoflavones of soybeans are genistein, daidzin and glycitin and they are structurally similar to 17-beta estradiol. They bind estrogen A and B receptors acting as incomplete estrogenic agonists [19].

Most of the studies about the lipid lowering effect of soy derivates, utilized a variety of soy products, differing amounts of soy protein,

Table 1
Official position statements and qualified opinions expressed by the European Food Safety Authority (EFSA) and U.S. Food and Drugs Administration (FDA) about the main nutraceuticals used for the treatment of hypercholesterolemia.

Substance	EFSA	FDA
Soy	A cause and effect relationship has not been established between the consumption of isolated soy protein and a reduction in blood LDL-cholesterol concentrations. [92]	The addition of soy protein to a diet that is low in saturated fat and cholesterol may help to reduce the risk of CHD. The food product shall contain at least 6.25 g of soy protein per reference amount customarily consumed of the food product. [93]
Dietary fibers	No established cause and effect relationship between the consumption of dietary fiber and blood cholesterol concentration. [94]	The addition of soluble fiber to a diet that is low in saturated fat and cholesterol may help to reduce the risk of CHD. Dietary intake levels associated with reduced risk of CHD are: – ≥3 g/day of [beta]-glucan soluble fiber from either whole oats or barley, or a combination of whole oats and barley. – ≥7 g/day of soluble fiber from psyllium seed husk. [95]
Plant sterols & stanols	A daily intake of 3 g (range: 2.6–3.4 g) in matrices approved by the Regulation (EC) No. 376/2010 (yellow fat spreads, dairy products, mayonnaise and salad dressings) lowers LDL-cholesterol by 11.3% (95% CI: 10.0–12.5). The minimum duration required to achieve the maximum effect on LDL-cholesterol lowering is 2 to 3 weeks. [96]	Plant sterol/stanol esters may reduce the risk of CHD. Plant sterol/stanol esters in the diet help to lower blood total and LDL cholesterol levels. Daily dietary intake levels associated with reduced risk of CHD are: – ≥1.3 g/day of plant sterol esters. – ≥3.4 g/day of plant stanol esters. [97]
Policosanol	Inconsistent effects on total and LDL-cholesterol concentrations; there is no evidence of a mechanism by which policosanols from sugar cane wax could exert the claimed effect. A cause and effect relationship has not been established between the consumption of policosanols from sugar cane wax and maintenance of normal blood LDL-cholesterol concentrations. [98]	This product is not intended to diagnose, treat, cure, or prevent any disease. [99]
Red yeast rice	A cause and effect relationship has been established between the consumption of monacolin K from red yeast rice and maintenance of normal blood LDL cholesterol concentrations. Daily dietary intake levels associated with the claimed effect: 10 mg of monacolin K from fermented red yeast rice preparations. [100]	The red yeast rice powder contains greater than 0.4% lovastatin (monacolin K). The U.S. District Court for the District of Utah affirmed that red yeast rice products that contain significant amounts of lovastatin are subject to regulation as drugs and are not dietary supplements. [101]
Berberine	No publication available.	This product is not intended to diagnose, treat, cure, or prevent disease. [102]