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Review

Lipid-modifying effects of nutraceuticals: An evidence-based approach

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ABSTRACT

The present review provides an up-to-date summary of the findings on the lipid-lowering effects of the most important nutraceuticals and functional foods. Based on current knowledge, nutraceuticals might exert significant lipid-lowering, and their use has several advantages:

- They have natural origins and are mainly extracted from natural products.
- They are mostly safe and very well tolerated.
- Their use is supported by the findings from randomized controlled trials and meta-analyses.
- The lipid-lowering effect of most nutraceuticals is multimechanistic, which makes them potential candidates for improving the effects of current lipid-lowering drugs when used in combination.

A number of important questions remain to be addressed, including whether longer durations of therapy would result in a better response and the exact safety profile of nutraceuticals, especially at doses higher than those consumed in an average diet. Additionally, data regarding the effects of nutraceutical supplementation on the incidence of cardiovascular outcomes are lacking, and it is not clear whether additional lipid lowering by nutraceuticals can modify the residual cardiovascular risk that remains after statin therapy.

Introduction

Despite the undisputed role of statins in the treatment of dyslipidemia, searching for new lipid-modifying agents remains a growing interest [1–8]. This is in part due to the residual cardiovascular (CV) risk even after intensive statin therapy, inability to consistently achieve low-density lipoprotein cholesterol (LDL-C) goals, and statin-induced myopathy/myalgia occurring in 5% to 15% of treated patients [9–13]. There also is a lack of effective combination therapy for dyslipidemias as a result of negative results of studies [14]. The past two decades have witnessed a surge of interest in finding natural products with lipid-regulating activities [1,2,15–17]. The use of nutraceuticals and functional foods as adjuncts to standard pharmacotherapy has been adopted and recommended by most international guidelines including the National Cholesterol Education Program

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and the European guidelines of the management of dyslipidemias [18,19]. Apart from efficacy, the use of nutraceuticals may be advantageous in terms of safety and tolerance, although it is important to consider in what amount they are consumed in a normal diet and what is needed to improve the lipid profile [20].

A number of nutraceuticals have shown promising effects in terms of improving the lipid profile and modifying CV risk [21,22]. More importantly, there have been pooled analyses confirming the lipid-lowering efficacy of selected natural products in clinical settings (Table 1). The present review considers the most recently reported lipid-modifying effects of some important nutraceuticals.

Given the increasing demand for lipid-lowering agents of natural origin, the present review highlighted recent findings on the effects of nutraceuticals on plasma lipid indices, possible mechanisms of action, and safety data. Keeping in view the translational importance of clinical studies, this review focuses on agents with documented efficacy in randomized controlled trials (RCTs), pooled clinical analyses, or both.

Search strategy

We searched using electronic databases (MEDLINE: 1966 March 1, 2016; EMBASE and SCOPUS: 1965 to 2015; DARE: 2016; and Web of Science Core Collection: 2016). Additionally, abstracts from national and international meetings were searched. When necessary, the relevant authors were contacted to obtain further data. The main search terms were *nutraceutical(s), functional food(s), atherosclerosis, lipids, lipoporoteins, dyslipide(a)mia, low-density lipoprotein* (*LDL*), *LDL, LDL-C,* and *lipid disorders*. The main inclusion criterion was the existence of relatively strong data from studies, trials, and meta-analyses confirming the effectiveness of the given nutraceutical on lipid profile.

Plant sterols/stanols

Plant sterols and stanols are naturally occurring steroid derivatives that resemble cholesterol in structure and function. Plant sterols (mainly sitosterol and campesterol) and stanols (mainly sitostanol and campestanol) occur in several plant-based foods, most notably in vegetable oils, nuts, breeds, seeds, margarines, cereals, vegetables, and fruits [41,42]. The average dietary intake of plant sterols/stanols is between 200 and 400 mg/d, being higher in men than women [43–45]. Higher intakes can be achieved through consumption of phytosterol/phytostanol-enriched food products (vegetable oils, nuts, cereal products, fruit, and berries) or adherence to a vegetarian diet [46,47]. Experimental and clinical evidence has shown that plant sterols/stanols can ameliorate plasma levels of total cholesterol (TC), LDL-C, and triacylglycerols (TGs) [48].

The most robust mechanism for the hypolipidemic actions of plant sterols/stanols is through inhibition of intestinal absorption of cholesterol. Because phytosterols/phytostanols and cholesterol are absorbed via a common mechanism, increased consumption of the former compounds replaces cholesterol in the intestinal micelles, thereby reducing entrance of cholesterol into enterocytes and chylomicrons [49,50]. Unlike cholesterol, only a small fraction of sterols/stanols is assembled into chylomicron particles and the major content is pumped back to the lumen via the action of adenosine 5′-triphosphate–binding cassette transporters G5 and G8 (ABCG5/ABCG8) [51]. This leads to a low occurrence of sterols/stanols in plasma, which decreases their atherogenicity at high doses of dietary intake [51,52].

A recent report from the European Atherosclerosis Society Consensus Panel on Phytosterols has recommended the use of oral plant sterols/stanols ($\leq$2 g/d) in combination with lifestyle modification in patients at all stages of CV risk, in statin-intolerant patients, and also as adjunct to statin therapy in patients not at LDL-C target [48]. The magnitude of LDL-C reduction by plant sterols/stanols (at a dose of 2 g/d) has been estimated to be around 8% to 10%. There have been reports of TG levels being lowered by 6% to 9% with no appreciable effect on high-density lipoprotein cholesterol (HDL-C) [53].

A recent meta-analysis investigated the dose–response effect of combined and separate forms of plant sterols and stanols in 124 RCTs. The results indicated a clear dose–response effect in lowering LDL-C levels by doses $\leq$3 g/d, which resulted in LDL-C reductions between 6% and 12% [54]. LDL-C–lowering activity of plant sterols and stanols are comparable at doses $\leq$3 g/d, whereas there is some evidence that suggests a greater effect of stanols versus sterols at doses >4 g/d [54]. However, another meta-analysis reported no significant difference between supplemental and food-enriched phytosterol/phytostanol products in terms of reducing plasma LDL-C concentrations [55]. Data from long-term trials have validated the safety of plant sterols/stanols, especially at the recommended doses ($\approx$2 g/d) [56]. The issue regarding potential atherogenicity of plant sterols—mainly derived from reported associations between serum sterol levels and cardiovascular risk in epidemiologic and Mendelian randomization studies [57,58]—appears to be resolved owing to the evidence indicating that serum sterol levels reflect cholesterol absorption [59] and are not atherogenic by themselves [58,60,61]. A number of trials have shown a reduction in certain fat-soluble vitamins (in particular α-tocopherol) after phytosterol supplementation, which can be compensated by increased fruit and vegetable consumption [48,62,63].

Berberine

Berberine is an isoquinoline-type alkaloid occurring naturally in plants like *Coptis*, goldenseal, and several *Berberis* species such as barberry (*Berberis vulgaris*), Oregon grape (*Berberis aquifolium*), and tree turmeric (*Berberis aristata*) [64]. In vitro and in vivo findings have revealed several beneficial metabolic actions for berberine, including attenuation of insulin resistance, obesity, and atherogenic dyslipidemia [65]. The lipid-lowering effects of berberine have been mostly attributed to the upregulation of LDL receptor (LDLR) expression, as well as increasing LDLR half-life [66,67]. The latter effect has been suggested to be the result of proprotein convertase subtilisin-kexin type 9 (PCSK9) downregulations by berberine [68–70]. Moreover, activation of 5′-adenosine monophosphate-activated protein kinase (AMPK) and inhibition of the mitogen-activated protein kinase/extracellular signal-regulated kinase pathway may account for part of the LDL-C- and TG-lowering effects of berberine [71].

In a recent meta-analysis including 11 RCTs with individuals with hypercholesterolemia, type 2 diabetes, or both, supplementation with berberine was found to exert a favorable effect on plasma lipid profile by decreasing TC (by 23 mg/dL; $P < 0.001$), LDL-C (by 25 mg/dL; $P < 0.001$), and TG (by 40 mg/dL; $P < 0.001$), while increasing HDL-C (by 2 mg/dL; $P = 0.001$) concentrations [24]. In addition to monotherapy, the berberine-simvastatin combination caused significant additional reductions in total TC (18%), LDL-C (20%), and TG (28%), and elevation in HDL-C (5%) concentrations compared with simvastatin monotherapy [72].