SHORT COMMUNICATION

Utilizing nutraceuticals with lipid-lowering properties for an integrative strategy in managing dyslipidemia

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ABSTRACT

Dyslipidemia, a modifiable risk factor for atherosclerotic cardiovascular disease, can be effectively addressed through lifestyle modifications and/or lipid-lowering therapies. However, the clinical use of statins may pose challenges for some patients due to potential side effects such as statin-associated muscle symptoms. Consequently, there is a growing interest in integrative cardiology and the use of nutraceuticals as an alternative or complementary approach to managing dyslipidemia. This interest is driven by patients seeking a more natural approach to their condition.

In this context, nutraceuticals have garnered attention as potential agents for dyslipidemia management, both in patients with and without established atherosclerotic cardiovascular disease. To shed light on this area, we present an updated review of the evidence surrounding various new and emerging nutraceuticals. We delve into their mechanism of action, lipid-lowering effects, and potential side effects. Some of these nutraceuticals include red yeast rice, bergamot, and others.

Key Words: *Dyslipidemia; Cardiovascular risk reduction; Complementary medicine; Integrative medicine; Lipoprotein (a)*

INTRODUCTION

Atherosclerotic Cardiovascular Disease (ASCVD) pertains to the accumulation of plaque within arteries, resulting in various cardiovascular issues such as cerebrovascular disease and peripheral arterial disease. The development of ASCVD involves a complex interplay of several factors. Among these factors, chronic inflammation plays a crucial role and also contributes to the erosion and rupture of unstable plaque [1]. Another significant aspect in the pathogenesis of ASCVD is endothelial dysfunction, which is primarily influenced by nitric oxide and prostacyclins [1]. Evaluating endothelial dysfunction non-invasively can be achieved through Flow-Mediated Dilation (FMD), although additional research is necessary to understand the impact of dyslipidemia on FMD values [1]. Diabetes Mellitus Type 2 (DM2) represents another risk factor linked to both microvascular and macrovascular diseases. It is also associated with lower levels of High-Density Lipoprotein Cholesterol (HDL-C) and elevated Triglycerides (TG), nitrotyrosine, nitrated Low-Density Lipoprotein-Cholesterol (LDL-C), and nitrated HDL-C, which collectively increase the risk of cardiovascular disease.

Dyslipidemia represents a significant modifiable risk factor for ASCVD, with an approximate global prevalence of elevated cholesterol estimated at 40% according to the World Health Organization [2]. Longitudinal studies have strongly linked a lifetime exposure to elevated LDL-C. It is crucial to assess patients with an LDL-C level ≥ 4.91 mmol/L (≥190 mg/dL) for familial hypercholesterolemia, a frequently underdiagnosed condition wherein around 85% of individuals with this autosomal dominant genetic disorder remain unaware of their diagnosis [2]. Additionally, there are other abnormalities in the lipid profile that may be considered as risk-enhancing factors, signaling the need for initiating or intensifying therapy in specific patients.

NUTRACEUTICALS AND THEIR MAIN EFFECTS ON LDL-C

1. **Red yeast rice extract**

   Red Yeast Rice (RYR) extract, a traditional Chinese supplement, is produced by fermenting yeast (*Monascus purpureus*) on white rice and contains various compounds such as sterols, isoflavones, and polyketides, with one prominent component being monacolin K. The structure of monacolin K's lactone form is identical to that of lovastatin, and its activation into the active hydroxyl acid form occurs through conversion in the small intestine and liver [3]. Consumption of RYR extract leads to a decrease in atherogenic LDL-C particles, resulting in a significant reduction in the risk of cardiovascular events.

2. **Berberine**

   Berberine is a quaternary benzylisoquinoline alkaloid

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widely used in China [3]. It can be extracted from various plant genera, including *Berberis*, *Coptis*, and *Hydrastis*, found in the bark, fruit, root, rhizome, and stem of these plants [3]. One of its key actions is the inhibition of PCSK9, leading to reduced degradation of the hepatic LDL receptor and consequently improved clearance of serum LDL-C [4]. Furthermore, berberine enhances the expression of the hepatic LDL receptor at the messenger ribonucleic acid level by activating the Jun amino-terminal kinase and extracellular signal-regulated kinases [4]. Additionally, it employs other secondary mechanisms such as reducing gastrointestinal reabsorption of cholesterol, promoting fecal excretion, and increasing hepatic bile acid formation [5].

3. **Garlic extract**

Garlic extract, derived from the herb garlic and used in traditional Indian and Chinese medicine, is available in various forms such as raw garlic, extracted oil, or powdered tablets. One of its key components is allicin (diallyl thiosulfinate), which has the ability to inhibit HMG-CoA reductase, acetyl-CoA synthetase, squalene-monooxygenase, and potentially non-acetylated CoA . Garlic has been associated with inhibiting the intestinal absorption of fatty acids and cholesterol, while also promoting the excretion of bile acids [6]. The typical dosage of garlic extract usually falls within the range of about 0.3 g to 20 g [6].The expected reduction in LDL-C with garlic extract consumption is typically between -5% to -10% [6]. A recent network meta-analysis of 26 Randomized Controlled Trials (RCTs) involving 1620 participants showed that those in the garlic arm experienced decreases in Total Cholesterol (TC), LDL-C, and Triglycerides (TG), along with an increase in High-Density Lipoprotein Cholesterol (HDL-C) compared to those in the placebo group [7]. Another meta-analysis of six trials revealed that garlic extract increased serum lipoprotein(a) (Lp(a)) levels by 54.59% in trials lasting longer than 12 weeks.

NUTRACEUTICALS AND THEIR EFFECTS ON OTHER LIPID TARGETS

Nutraceuticals, which are bioactive compounds derived from natural sources, have been studied for their potential effects on various lipid targets in the body. Here are some examples of nutraceuticals and their effects on different lipid targets:

1. **Polyunsaturated n-3 fatty acids**

Polyunsaturated n-3 fatty acids, such as Eicosapentaenoic Acid (EPA) and Docosahexaenoic Acid (DHA), are long-chain types of fats naturally occurring in various sources such as fish, krill, squid, eggs, algae, flaxseeds, walnuts, clary sage, and other edible seeds. The European Food Safety Authority (EFSA) recognizes that consuming EPA and DHA can potentially lead to reduced levels of triglycerides in the bloodstream [7].These particular PUFAs function by decreasing the production of hepatic VLDL (Very-Low-Density Lipoprotein), endogenous fatty acids, substrates available for triglyceride synthesis, and the activity of enzymes like diacylglycerol acyltransferase or phosphatidic acid phosphohydrolase, which play roles in triglyceride synthesis. Additionally, they promote the process of β-oxidation of fatty acids and increase the synthesis of phospholipids.

2. **Niacin**

Niacin, also known as nicotinic acid or vitamin B3, is utilized by many clinicians in the treatment of hypertriglyceridemia for patients who cannot tolerate statins, even though it is no longer recommended for reducing LDL-C levels [7]. Its mechanism involves inhibiting diacylglycerol acyltransferase-2, leading to decreased synthesis of triglycerides and LDL-C levels by promoting the degradation of hepatic *ApoB*. Additionally, niacin raises HDL-C levels by stimulating the production of hepatic apolipoprotein A-I [7]. Typical daily dosages are kept at or below 2 grams.

3. **L-Carnitine**

L-Carnitine is a hydrophilic quaternary ammonium cation naturally present in meat, fish, poultry, and dairy products. It is also synthesized in the brain, liver, and kidneys. When combined with coenzyme Q10, L-carnitine supplementation may potentially reduce SAMS. The effects of L-carnitine include a decrease in Triglyceride (TG) synthesis by reducing available free fatty acids, an increase in mitochondrial oxidation of long-chain fatty acids, and an enhancement in the production of apolipoprotein A1. Typical oral dosages range from 500 mg to 3 g, and in some cases, it can be as high as 6 g per day [8]. A meta-analysis involving 55 Randomized Controlled Trials (RCTs) with 3058 participants revealed that those who received L-carnitine supplementation experienced reductions in total cholesterol (TC) by -0.22 mmol/L (95% CI, -0.35 to -0.09), low-density lipoprotein cholesterol (LDL-C) by -0.14 mmol/L (95% CI, -0.22 to -0.06), and TG by -0.11 mmol/L (95% CI, -0.18 to -0.03), along with an increase in High-Density Lipoprotein Cholesterol (HDL-C) by 0.04 mmol/L (95% CI, 0.01 to 0.07). The analysis also indicated that higher doses of L-carnitine (≥2 g) resulted in a greater reduction in TC and LDL-C.In another meta-analysis consisting of four RCTs involving 218 participants, oral L-arginine supplementation was found to lower Lp(a) by -0.09 mmol/L (95% CI, -0.10 to -0.08).

INCONSISTENT DATA REGARDING NUTRACEUTICALS AND DYSLIPIDEMIA

1. **Resveratrol**

Resveratrol, also known as 3,5,40-trihydroxystilbene, is a non-flavonoid polyphenol found primarily in red grapes, raspberries, mulberries, blueberries, knotweed, peanuts, as well as in certain juices and wines derived from these fruits [8]. This compound has been attributed with potential antioxidant, anti-inflammatory, anti-apoptotic,

and anti-cancer properties. Resveratrol activates the silent information regulation 2 homolog 1 and has been demonstrated to inhibit the upregulation of hepatic genes associated with lipogenesis while preventing the downregulation of genes involved in lipolysis [8]. Additionally, it may have a positive effect on atherosclerosis by suppressing foam cell formation. Standard dosages typically range from 250 to 3000 mg per day .

2. **Curcumin**
   Curcumin, a yellow polyphenolic compound, is naturally present in the dried rhizomes of turmeric (*Curcuma longa*), native to Southeast Asia [9]. It has a rich history in traditional Chinese and Indian medicine and has found various commercial applications, including its use as a food additive and in cosmetics [10]. Curcumin exerts its effects on cholesterol metabolism by inhibiting the expression of intestinal NPC1L1 cholesterol transporter through the inhibition of the SREBP2 transcription factor. Additionally, it enhances the clearance of LDL-C by increasing the expression of LDL receptors, achieved by downregulating PCSK9 expression. Furthermore, curcumin promotes cholesterol efflux by upregulating ABCA1 expression. Typical dosages of curcumin can vary from 50 mg to 6 g per day.

LIFESTYLE CHANGES AND THE IMPACT ON DYSLIPIDEMIA

Lifestyle changes play a crucial role in managing dyslipidemia, which is characterized by abnormal levels of lipids in the blood, such as cholesterol and triglycerides. Implementing healthy lifestyle practices can effectively reduce lipid levels and decrease the risk of cardiovascular disease. Some key lifestyle changes and their impact on dyslipidemia include:

1. **Healthy diet**
   Adopting a balanced diet low in saturated fats, trans fats, and cholesterol can help improve lipid profiles. Emphasizing fruits, vegetables, whole grains, and lean proteins, while limiting processed and high-fat foods, can lead to lower LDL cholesterol and triglyceride levels.

2. **Regular physical activity**
   Engaging in regular aerobic exercises, such as walking, jogging, swimming, or cycling, can increase HDL cholesterol (the "good" cholesterol) and improve overall lipid profiles. Physical activity also aids in weight management, which is essential for lipid control.

3. **Weight management**
   Maintaining a healthy weight or achieving weight loss (if overweight or obese) can positively impact lipid levels. Weight loss is particularly beneficial for reducing triglyceride levels and increasing HDL cholesterol.

4. **Smoking cessation**
   Quitting smoking is vital for managing dyslipidemia. Smoking can lower HDL cholesterol levels and damage blood vessels, further elevating cardiovascular risk.

5. **Limit alcohol intake** Moderating alcohol consumption or avoiding it altogether can help control triglyceride levels and prevent other detrimental effects on lipid profiles.

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