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Bergamot extract and red yeast rice in reducing high cholesterol -what is known?

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Abstract

Obtaining optimal levels of lipoproteins and total cholesterol is one of the main goals for reducing cardiovascular risk. Many patients insist on changing their statin treatment to a nutraceutical such as Bergamot extract or red yeast rice extract, due to statin intolerance affecting some of them and increasing disinformation on statin side effects. This is why, interest in lipid-lowering ability of available nutraceuticals, is growing.

In our work, we tried to summarise what is known about nutraceuticals such as red yeast rice and bergamot extract and how they can be used in clinical practise.

We searched two databases such us Pubmed and Medline byusing the terms “bergamot”, ”red yeast rice”, “dyslipidaemia” and “hypercholesterolaemia”
Products containing red yeast rice and bergamot extract are dietary supplements which are sold over the counter. There is possibility that they can be seen as natural substances which significantly reduce cholesterol levels, however, they have weaker effect than strong statins. They cannot be replacement for them.
Red yeast rice is the leading substance. It can be used in patients with moderate hypercholesterolemia or can be combined with ezetimibe if statins are badly tolerated. There is no clear opinion of experts on bergamot due to lack of larger and longer studies.
As our article show it is crucial to conduct more scientific research on nutraceuticals especially Bergamot extract.

KEY WORDS: hypercholesterolemia; dyslipidemia; Citrus bergamia

Introduction

Hypercholesterolemia has no clear and universally accepted definition for the time being. Periodic blood lipid measurements and the reduction of levels of circulating atherogenic lipoproteins are significant procedures to reduce the beginning or recurrence of atherosclerotic cardiovascular disease. Thus, by lowering levels of lipid in the blood pharmacologically, the risk of atherosclerotic cardiovascular disease can be reduced significantly. Threshold levels of low-density lipoprotein cholesterol (LDLc) concentration and individual atherosclerotic cardiovascular disease risk are indicators for treatment used in current clinical guidelines.[1–4]

Statins are a class of drugs frequently prescribed to lower cholesterol. Some patients, who takes statins, report side effects such us myalgia, crumps and proximal muscle weakness. Adverse effects on skeletal muscles occur in approximately 5–10% of patients taking statins. These symptoms, in combination with possible disease entity which can be associated with taking statins such as diabetes mellitus, acute kidney injury, tendon rapture and rhabdomyolysis, cause that some patients reluctantly take this medication or even refuse doing it.[5–7]

In the internet, bergamot extract and red yeast rice are presented as natural supplements with the ability to lower cholesterol, hence some patients ask if they can take them instead of

statins. Thus, the goal of this article is to evaluate the clinical evidence for effectiveness of this supplements as a strategy for improving dyslipidemia.

Bergamot (Citrus Bergamia)

The Bergamot is a citrus fruit from southern Italy that is traditionally used to improve cardiovascular function and immune system. Its peel essential oils are used in the cosmeic, perfume and pharmaceutical industry. It juice has anti-inflammatory, antioxidant and cholesterol reducing function.[8–12]

This fruit contains high content of flavonoids such as diometin 6,8-di-C-glucoside, lucenin-2, vicenin-2 (which belong to C-glucoside flavonoids), brutieridin, melitidin, rhoifolin 40-O-glucoside (which belong to flavone O-glycosides), naringin, neohesperidin and neoeriocitrin, [8,13–17]

It was shown in studies that neoeriotrin, naringin and rutin have antioxidant activity. [8,18] In another study rabbits were fed a high cholesterol diet and divided into three groups (1. Placebo, 2. naringin, 3. lovastatin). Those which were given naringin had significant reduction in fatty streak formation and macrophage infiltration in endothelial cells. [8,19]

There are two possible mechanisms of action of bergamot. One of them is inhibition of LDL cholesterol oxidation and the adenosine-monophosphate-kinase activation. Another is an increased cholesterol elimination with faeces by lowering its absorption in intestine and increasing the turnover and excretion of bile acids. [12,20,21]

There are not many studies regarding the hypolipidemic properties of bergamot extract, although those that are available are promising. [12]

Randomized, double-blind, placebo-controlled study conducted on 60 patients by Mollace et al. showed significantly modified cholesterol levels after 30 days in people who was given bergamot polyphenol fraction and bergamot polyphenol fraction phytosomal formulation. Subjects, depending on which group they belonged to, received twice daily 650mg in polyphenol fraction group and 500 mg in polyphenol fraction phytosomal formulation group. In both groups there were similar results. In polyphenol fraction total cholesterol was lowered from 262 to 196, LDL cholesterol from 175 to 116, triglycerides from 252 to 170 and HDL cholesterol increased from 44 to 48. In polyphenol fraction phytosomal formulation group from 261 to 198, from 174 to113, from 252 to 173 and from 44 to 50 respectively. [8,22]

In 12 analysed studies by Lamiquiz-Moneo et al, in which 870 adults aged 27-77 taken part, it was observed that total cholesterol reduction ranged between 12.3% and 31.3%, triglycerides between 11.5% and 39.5% and LDL-c between 7.6% and 40.8%. Bergamot extract doses ranged from 500 mg/day to 1500 mg/day while the intervention duration ranged from 1 month to 6 months. [12,23]

Other randomized, double-blind, placebo-controlled study conducted on 237 patients, who taken 500 mg, 1000 mg or 1500 mg bergamot fractions per day for 30 days, by Mollace et al. showed reduction in total cholesterol by 21.8% (500 mg of bergamot) and 29.4% (1000 mg of bergamot), in LDL-c by 24.1% and 30.6% and increase in HDL by 22.3% and by 40.1% respectively. In patients with higher triglycerides level, the reduction of lipids by 28.2% in the group treated with bergamot at 500 mg/day and 37.9% in the group taking 1000 mg/day was observed. There were a group of patients, who stopped the statin treatment due to adverse reactions and took 1500 mg of bergamot per day, with a reduction of LDL-c and triglycerides levels to 27.6% and 25%, respectively. [8,12,24]

Another clinical study conducted on 80 human subjects, which received 150 mg of bergamot flavonoids daily for 6 months, by Toth et al revealed reduction of total cholesterol (from 255 to 224), LDL cholesterol (from 159 to 132), triglycerides (from 159 to 133) and increase in HDL cholesterol (from 50 to 54). [8,21]

Clinical trial on 11 participants by Babish et al evaluated that 500 mg of bergamot fruit extract taken daily for 12 weeks decreased total cholesterol by 7.3 %, LDL cholesterol by 10% and apolipoprotein B by 2.8%. Changes in levels of HDL and triglycerides were not statistically significant. [8,25]

In meta-analysis based on 131 trials enrolling 13062 participants by Osadnik et al it was shown that in terms of LDL-c and triglycerides reduction the most effective nutraceuticals are bergamot and red yeast rice. [26] Similar results regarding bergamot extract were obtain in a meta-analysis by Cicero et al. [27]

There is also available study conducted on mice and rats. 1 ml of bergamot juice per day for 30 days were administered to rats with diet-induced hypercholesterolemia. It resulted in reduction of total cholesterol concentration (29.3%), triglycerides (46%), LDL cholesterol (51.7%) and increase of HDL cholesterol (27.6%). [12,28]

Study, reference	Study population	Dose of substance	Findings
Bergamot			
Mollace et al.[22]	60 patients	Twice daily 650mg of bergamot polyphenol fraction in group 1 and twice daily 500 mg of bergamot polyphenol fraction phytosomal formulation in group 2	Bergamot polyphenol fraction group: reduction of total cholesterol from 262 to 196, LDL-c from 175 to 116, triglycerides from 252 to 170 and increase of HDL-c from 44 to 48. Bergamot polyphenol fraction phytosomal formulation group from 261 to 198, from 174 to113, from 252 to 173 and from 44 to 50 respectively.
Mollace et al. [24]	237 patients	500 mg, 1000 mg or 1500 mg	Reduction in total cholesterol by 21.8% (500 mg of bergamot) and 29.4% (1000 mg of bergamot), in LDL-c by 24.1% and 30.6% and increase in HDL by 22.3% and by 40.1% respectively.
Toth et al. [21]	80 patients	150 mg of bergamot flavonoids	Reduction of total cholesterol (from 255 to 224), LDL cholesterol (from 159 to 132), triglycerides (from 159 to 133) and increase in HDL cholesterol

			(from 50 to 54).
Babish et al.[25]	11 patients	500 mg of bergamot fruit extract	Reduction of total cholesterol by 7.3 %, LDL cholesterol by 10% and apolipoprotein B by 2.8%. Changes in levels of HDL and triglycerides were not statistically significant.
Red yeast rice			
Minamizuka et al. [29]	18 patients	-	Significant reduction in LDL-c, total cholesterol, apolipoprotein B, without any adverse effect
Chen et al. [30]	117 patients	1 tea bag containing 4 mg/g monacolin K β-hydroxy acid form (MKA)	MKA along with lifestyle modifications caused a significant decrease in LDL-C by 15.6% on average, decrease in total cholesterol by 15.3% on average and a decrease in non-HDL-C by 35.4%.
Verhoeven et al. [31]	52 physicians	5,025 mg of Monacolin K	Reduction of LDL-c was lowered with 36 mg/dL (22%) and total cholesterol with 37 mg/dL (15%) in the intervention group.
Bogsrud et al. [32]	40 patients	4.8 mg monakolin K in the lactone form and 2.4 mg monakolin K in the hydroxyl-acid form	Reduction in LDL-cholesterol (23.0%) and total cholesterol (15.5%) compared to placebo after 16 weeks of treatment.
Heinz et al. [33]	142 patients	3 mg monacolin K and 200 μg folic acid per day.	Reduction of LDL-C (−14.8%), total cholesterol (−11.2%), and homocysteine (−12.5%)

Table 1. Studies on effect of bergamot extract and red yeast rice on dyslipidaemia.

Red yeast rice

For many centuries red yeast rice has been used in Asian countries in medicine and also as colouring agent. This substance is obtained through subjecting regular rice to the process of fermentation with the Monascus purpureus which belong to the mould species. During fermentation substances, such as monacolin K and citrinin, are produced. Monacolin K is structurally identical to lovastatin and inhibits 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase which is responsible for cholesterol synthesis in the liver. [12,34,35]

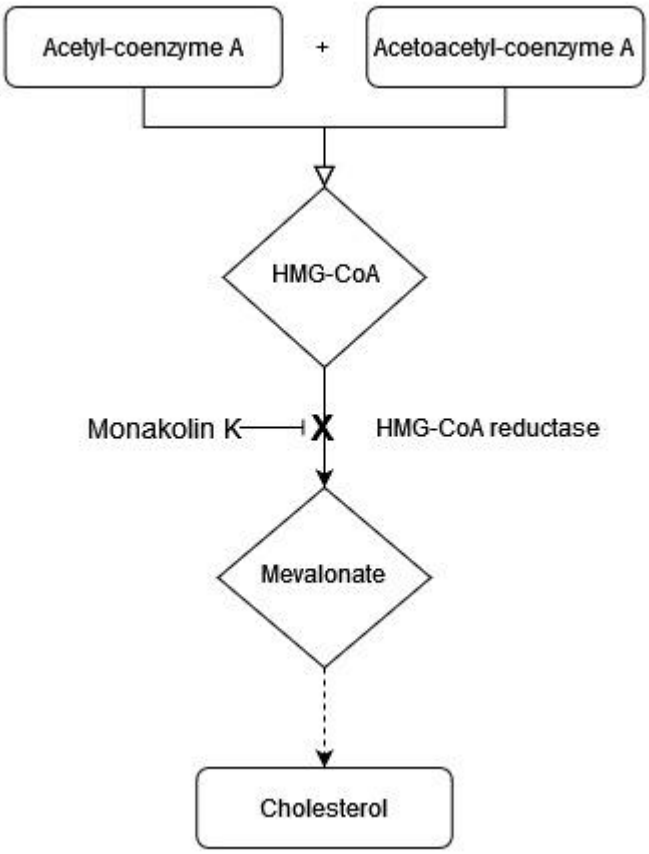

Figure 1. Cholesterol-lowering mechanism of red yeast rice.[36]
HMG-CoA- Hydroxy-methyl-glutaryl-coenzyme A; RYR- red yeast rice

The problem is that red yeast rice is available as a dietary supplement therefore, it is not standardised. In some cases the monacolin K can be in different doses than those declared by manufacturer and there is no certainty citrinin is not present. Citrinin should not be in any

amount because it causes kidney damage such as glomerular endothelial hyperplasia and increased risk of adenomas. [12,37,38]

Chinese Coronary Secondary Prevention Study in which participated 4870 patients aged 18-75 years post-myocardial infarction from 66 hospitals showed total cholesterol reduction by 10%, LDL-C by 17.6%,triglycerides by 15.2% and increase I HDL-c by 4.2%. Patients were given purified red yeast rice extract, 600 mg twice a day for 4 years and placebo. There were noticed some side effects such as a non-significant increase in the liver and kidney markers. [12,39,40]

A multicentre randomized trial by Minamizuka et al., on 18 patients without know cardiovascular disease and with unsatisfactory low-density lipoprotein cholesterol, found significant reduction in LDL-c, total cholesterol, apolipoprotein B, without any adverse effect, in the group of patients taking red yeast rice.[29]

Meta-analysis of 7 Chinese double-blind clinical studies with 10699 patients post-myocardial infarction, aged 50-70 years with hypercholesterolemia assessed that there were significantly fewer non-fatal myocardial infarctions and significant difference in revascularisation procedures among patients taking red yeast rice compared to placebo. In 6 clinical studies the weighted men of the LDL-c level difference between patients taking red yeast rice and those on placebo amounted to -20.7 mg/dl, total cholesterol -26.61 mg/dl and triglycerides -24.69 mg/dl, HDL-C +2.71 mg/dl. Patients were receiving 1200 mg per day for period ranging from 6 weeks to 4.5 years. 4 out of 7 studies raised the issue of red yeast rice safety. It was noticed that there were no differences in the incidence of severe adverse events compared to control groups. [12,41]

Meta-analysis by Gerards et al. on 6663 subjects from 20 studies revealed that in studies without active control LDL-c level reduction in patients taking red yeast rice ranged from 0.5 to 1.59 mml/L, however in studies controlled with statins (pravastatin 40 mg/d, simvastatin 10 mg/d, lovastatin 20 mg/d) there were no significant differences in lipid levels. The authors of meta-analysis concluded that red yeast rice have clinically and statistically significant effect on LDL-c reduction and it “could be safe and effective therapeutic option for treatment of dyslipidaemia for statin-intolerant patients”[12,42]

Meta-analysis of 53 randomised control studies, which included 4437 patients taking red yest rice and 4303 in control group, evaluated the safety of monacolin K. The results showed that there was no increased risk of severe adverse reactions in patients taking red yeast rice compared to the control group. [12,43]

The meta-analysis performed by Pengfan et al. resulted in conclusion that red yeast rice was comparable to regular statin treatment regarding LDL-c reduction, less effective in terms of total cholesterol reduction and more effective regarding triglycerides reduction. [26,44]

Product	Daily doses	LDL-c reduction	Adverse reactions
Bergamot	50-1500 mg	15%-25%	None observed
Red yeast rice	1200-4800 mg	15%-25%	Typical for statins, dependent on monacolin dose.

Table 2. Bergamot extract and red yeast rice in statin-intolerant patients.[12]

Conclusions

Obtaining optimal levels of lipoproteins and total cholesterol is one of the main goals for reducing cardiovascular risk. Many patients insist on changing their statin treatment to a nutraceutical such as Bergamot extract or red yeast rice extract, due to statin intolerance affecting some patients and increasing disinformation on statin side effects. This is why, interest in lipid-lowering ability of available nutraceuticals, is growing.

Many preclinical and clinical evidences of efficacy and safety, support usage of lipid-lowering nutraceuticals. However, this kind of therapy should never be substitution of conventional drugs indicated by the international guidelines. [45]

Products containing red yeast rice and bergamot extract are dietary supplements which are sold over the counter. There is possibility that they can be seen as natural substances which

significantly reduce cholesterol levels, however, they have weaker effect than strong statins. They cannot be replacement for them.

Among the nutraceuticals with cholesterol lowering properties, red yeast rice is the leading substance. It can be used in patients with moderate hypercholesterolemia or can be combined with ezetimibe if statins are badly tolerated (class I, level of evidence A). It can be also used in patients with mild and moderate hypercholesterolemia, as an adjunct to diet therapy in primary prevention of cardiovascular diseases. There is no clear opinion of experts on bergamot due to lack of larger and longer studies. [12,46,47]

In our work, we tried to summarise what is known about nutraceuticals such as red yeast rice and bergamot extract and how they can be used in clinical practise.

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