

Bergamot Polyphenols: A Phytotherapeutic Approach to Hyperlipidemia and Hypercholesterolemia Control

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ABSTRACT

Bergamot is a citrus fruit, typical of Calabria and produced in the narrow strip of the Reggio Calabria's coast. It is appreciated for its cosmetic properties, although it was sometimes used for its antiseptic and antibacterial action in ophthalmology, gynecology and dermatology. The discovery of its hypolipidemic and hypoglycemic activity is recent. Bergamot helps to control cholesterol and triglyceride levels. It also exerts antioxidant actions on the endothelium. Bergamot essential oil may represent a viable alternative for all those patients who are suffering from side effects of statins or cannot reach the therapeutic target for the pharmacological treatment, thanking to its high content in phenols and its lipid-lowering and glucose-lowering properties. The anti-oxidant properties can ameliorate endothelial cardiovascular disorders.

Keywords: Bergamot, dyslipidaemia, anti-oxidant, lipid-lowering agents

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INTRODUCTION

Dyslipidaemia is an important risk factor for the development of atherosclerosis and coronary artery disease^{1,2}.

Statins represent the gold standard therapeutic protocol adopted in order to reduce hypercholesterolemia^{3,4}. Their main action is to inhibit the activity of 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) reductase which is an enzyme able to catalyze the main rate-limiting step in mevalonate biosynthesis that is the transformation of HMG in mevalonic acid. This latter intermediate constitutes the precursor of the cholesterol. Despite the use of such potent pharmaceutical compound, many patients do not achieve their recommended low-density and high-density lipoprotein (LDL-C, HDL-C) cholesterol levels⁵. Moreover, statins cannot be used in more than 40% of patients because of side effects occurrence, such as myalgia, myopathy, liver disease and sometimes, rhabdomyolysis^{6,7}. These side effects limit the use of

statins and suggest the need of alternative therapeutic approaches⁸⁻¹⁰. The scientific evidences suggest that dietary polyphenols, in particular flavonoids, can prevent atherosclerosis through their anti-oxidative and anti-inflammatory properties⁸⁻¹². Furthermore, natural plant polyphenols seem to exert hypolipemic activities in both animal and human models thus, suggesting pleiotropic beneficial effects of such compound on cardiovascular system¹²⁻¹⁴.

Bergamot (*Citrus bergamia*) is an endemic plant that grows on the ionian coast of Calabria Region (Italy). Bergamot juice is rich in natural anti-oxidants and flavonoids^{15,16}. It contains for example, naringin, also identifiable in grapefruit which was demonstrated to reduce the atherosclerotic burden in animals¹⁷. Neohesperidin and rutin are further compounds present in the Bergamot and seem to inhibit LDL oxidation¹⁸.

Bergamot oil was firstly appreciated for its cosmetic properties and it was used for its antiseptic and antibacterial action in ophthalmology, gynecology and dermatology settings. Nevertheless, physicians recently demonstrated that it can exert hypolipemic and hypoglycemic activities thus, it can control cholesterol and triglyceride levels. Finally, it has also antioxidant actions on the endothelium.

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Among flavonoids contained in bergamot juice, it can be considered as the most important ones the following: Melitidine and brutieridine which possess a 3-hydroxy-3-methylglutaryl region similar to the natural substrate of HMG-CoA reductase^{19,20}.

The aim of this mini-review is to evaluate the role of Bergamot in the general management of patients suffering from dyslipidaemia.

HYPOLIPEMIC AND HYPOGLYCAEMIC ACTIVITY

Experimental evidences obtained in animal models²⁰⁻²² support the hypolipemic and vasoprotective effects of bergamot constituents. Few studies investigated the role of such compound in humans. Mollace *et al.*²³ evaluated the effect of bergamot-derived polyphenolic fraction (BPF) on Total Cholesterol (TC), LDL-C, HDL-C, Triglycerides (TG) and fasting glycemia by means of a randomized, double-blind, placebo-controlled study. In particular, they enrolled 237 patients who were subdivided in three groups: isolated hypercholesterolemia (group A), mixed hyperlipidemia (hypercholesterolemia/hypertriglyceridemia (group B) and metabolic syndrome (group C). The patients underwent administration of placebo or BPF daily (before meal) for 30 consecutive days. All of them showed a great reduction in lipids levels after the treatment period with a significant reduction in TC, LDL-C and TG and a corresponding increase in HDL-C blood concentrations. In addition, there was a reduction in blood glucose ranging from 15-25% in all groups²³.

Such a hypoglycaemic effect was related to the increased activity of the adenosine monophosphate (AMP) kinase involved in the glucose uptake in the liver and muscles²⁴. The naringenin contained in bergamot juice had a similar chemical structure to resveratrol and it is able to activate the sirtuin deacetylase-1 Nicotinamide Adenine Dinucleotide (NAD)-dependent enzyme which deacetylates proteins involved in cellular regulation to stress factors. The sirtuin 1 is inhibited in case of insulin resistance. Thus, by enhancing sirtuin-1 activity, naringenin increases the insulin sensitivity of the cells²⁵. Furthermore, naringenin demonstrated to promote glucose uptake through glucose transporter (GLUT-4) expressed in adipocytes and skeletal muscle. This increases the uptake of glucose into cells²⁶.

Furthermore, in order to assess the practical action of such a treatment on cardiovascular system, the patients underwent assessment of brachial artery Flow Mediated Vasodilatation (FMD) which revealed a great improvement in endothelial function

after 30 days treatment with both BPF dosage (5000 and 1000 mg daily). No changes were in placebo group²³. Gliozzi *et al.*²⁷ evaluated 77 patients suffering from mixed hypercholesterolemia and randomized to 5 groups with different treatment protocols (placebo, rosuvastatin 10 mg, rosuvastatin 20 mg, BPF 1000 mg, BPF 1000 mg plus rosuvastatin 10 mg). All groups underwent serum lipid profiles evaluation and urinary mevalonic acid (MVA) concentration, the latter in order to assess the real inhibition power of the HMG-CoA reductase inhibitors. Furthermore, the polymorphonuclear cells were isolated from the blood of each patient in order to evaluate the activity of lectin-like oxLDL receptor-1 (LOX-1), MDA levels (malondialdehyde, a marker of lipid peroxidation) and PKB (protein kinase B) phosphorylation degree²⁷. The association of BPF (1000 mg day⁻¹) with rosuvastatin (10 mg day⁻¹) for 30 consecutive days produced a significant improvement in lipid profiles as compared to basal levels and placebo group data. Specifically, the treatment with rosuvastatin 10 mg plus BPF produces a decrease in TC and LDL-C comparable to the effect of rosuvastatin 20 mg (TC: 172±3 mg dL⁻¹ vs 174±4 mg dL⁻¹; LDL-C: 90±4 mg dL⁻¹ vs 87±3 mg dL⁻¹)²⁷. In addition, triglycerides were reduced by 36±5%, while HDL-C increased by 37±2%. The BPF confirmed its vasoprotective properties in relation to the statistically significant decrease in the activity of LOX-1 and MDA levels observed by the authors²⁷.

Recent studies showed that the nonvolatile fraction of bergamot essential oil (Citrus Bergamia Risso and Poiteau) may lower blood lipid levels^{15,28,29}. The main constituents of Bergamot juice are natural antioxidants and are represented by the following compounds: Flavonoids (neohesperidin, neoeriocitrin, naringin, rhoifolin, rutin and neodesmin poncirin), furocoumarins (bergapten and bergamottin) and coumarins. In order to assess the total content of phenols in bergamot juice, the Folin-Ciocalteu reagent (a mixture in aqueous solution of phosphomolybdate and phosphotungstate used in analytical chemistry for the determination of phenols and polyphenols) can be used. It measured a total amount of about 2,474.35±38 µg mL⁻¹. Furthermore, the high-performance liquid chromatography allowed the evaluation of different flavonoids concentration: naringin 520 ppm, neoeriocitrin 370 and 310 ppm neohesperidin^{16,19,20}.

Among such compounds, neohesperidin and naringenin can exert the same function of statins: They possess a 3-hydroxy-3-methylglutaryl region similar at

the substrate of HMG-CoA reductase¹⁹. Therefore, their interaction with the enzyme is able to inhibit its action in the cholesterol metabolism pathway¹⁹. Finally, hesperetin seems to reduce the activity of enzymes involved in TG synthesis such as phosphatidate and phosphohydrolase, thus contributing in reducing the accumulation of triglycerides in the liver³⁰.

The beneficial effects attributed to the bergamot juice are also related to its anti-oxidant properties exerted by its content in polyphenols (flavonoids and coumarins). Polyphenols prevent Low-Density Lipoprotein (LDL) oxidation and foam cells formations. When compared to limonoids and bergapten, flavonoids had stronger antioxidant activity¹⁸. Several *in vitro* and *in vivo* studies demonstrated the above mentioned antioxidant and antiatherogenic effects.

Kaplan *et al.*³¹ evaluated the effects of pomegranate juice in atherosclerotic mice (deficient in apolipoprotein E), demonstrating a reduced cholesterol accumulation and foam cell genesis in mice fed PJ supplementation as compared to controls. Polyphenols seem to directly interact with the LDL, by scavenging reactive oxygen and reactive nitrogen species and to avoid the accumulation of such lipoproteins in circulating macrophages thus, indirectly preventing the formation of macrophage-rich peroxidized lipids (the so-called "foam cells"). Polyphenols can also induce the hydrolysis of the peroxidized lipids in the atherosclerotic lesions and increase the activity of the paraoxonase-1 enzyme^{31,32}. In particular, Bergamot juice can play important role in the treatment of vascular diseases, above all in stopping neointimal proliferation after percutaneous treatments. Mollace *et al.*²² demonstrated a reduced neointimal proliferation in the common carotid arteries of rats treated by means of balloon angioplasty. Such a result seemed to be mediated by the reduction in free radical formation and LOX-1 expression in a dose-dependent manner. LOX-1, in fact, usually contributes to intimal proliferation in damaged blood vessels; bergamot oil reduced its activity as well as the formation of peroxynitrite^{22,27,33,34}. Furthermore, naringin and naringenin can inhibit the expression of intracellular adhesion molecules (ICAM-1)^{17,35}. ICAM-1 is a transmembrane protein belonging to the family of immunoglobulins, typically expressed on endothelial cells and on lymphocytes³⁶. The activation of this protein under the stimulus of cytokines, produces pro-inflammatory effects by favoring the migration of leukocytes into tissues³⁶. The naringin-and naringenin-mediated ICAM-1 suppression may prevent the progression of atherosclerotic disease^{17,35,37}. Studying the effect of *C. Bergamia* administration in rats,

physicians observed a further reduction in TC and LDL-C, associated to an increased HDL-C concentrations: these results were due to the flavonoids of the juice which increased the natural sterols and total fecal bile acids excretion²⁰.

A recent study showed that Bergamot extracts represent a viable alternative to statins in patients intolerant to these drugs or in subjects discontinuing the treatment due to side effects. In 32 patients interrupting statin therapy due to the occurrence of side effects, Mollace *et al.*²² observed that a daily dose of 1,500 mg of bergamot juice extract induced in 30 of them a reduction of 25% in TC and 27.6% in LDL-C. No side effects were encountered although a small percentage of patients showed epigastric burning requiring treatment discontinuation²².

The extract of bergamot juice can improve endothelial function. It is well-established that endothelial dysfunction is associated to an increased cardiovascular risk and predispose individuals to further expression of atherosclerosis since childhood³⁸⁻⁴⁰. Brachial artery Flow-Mediated Vasodilatation (FMD) is the mostly used non-invasive test for assessing endothelial function^{41,42}. Hypercholesterolemic patients show a moderate endothelial dysfunction which can be much positively improved in case of treatment with capsules containing extract of bergamot juice²².

CONCLUSION

The synergistic effect of bergamot polyphenolic extract with statins may represent a potential benefit in reducing cardio-metabolic risk of individuals. Bergamot essential oil, due to its high content of phenols and its lipid-lowering and glucose-lowering properties may represent a viable alternative for all those patients who are suffering from side effects of statins or cannot reach the therapeutic target for the pharmacological treatment. Nevertheless, further studies are needed in order to definitely demonstrate the efficacy of such compound in clinical practice.

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