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The effect of bergamot on dyslipidemia

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ABSTRACT

Background: Statins are the most common used lipid lowering drugs but they may cause adverse effects and despite their well-established therapeutic benefits residual cardiovascular (CV) risk remains. The use of other lipid lowering drugs and nutraceuticals alone or as add-on lipid-modifying therapy can be an option in such cases. Several studies have reported health-related properties of the *Citrus* fruits, among which bergamot (*Citrus bergamia Risso)* differs from others by particularly high content of certain compounds.

Purpose: This narrative review summarizes the current evidence on the effects of bergamot on lipid parameters based on studies involving animals and humans.

Main evidence: This natural supplement may lead to effective lipid-lowering treatment. Its lipid-lowering activity is attributed to different flavonoids. However, the exact mechanisms involved remain unclear.

Conclusion: It is expected that ongoing and future studies will confirm the benefit of bergamot in dyslipidemic and other cardiometabolic disorders, potentially leading to reduced overall CV risk.

Introduction

Therapeutic approaches of dyslipidemia currently rely on the use of statins, pharmacological inhibitors of cholesterol biosynthesis that act on the key enzyme 3-hydroxy-3-methylglutaryl-Co-enzyme A (HMG-CoA) reductase (Athyros et al. 2014). Despite the fact that statin therapy reduces the incidence of major coronary events, coronary revascularization and stroke (Baigent et al. 2005), many patients, especially those with type 2 diabetes and metabolic syndrome (MetS), do not reach their lipid targets and remain at high cardiovascular (CV) risk (Jones 2008). Patients on statins may also have various side effects such as myalgia, myopathy or liver disease and rhabdomyolysis which interfere with adherence to treatment, especially if high doses of statins are required (Banach et al. 2015a, 2015b). New-onset diabetes (NOD) is another important issue to consider in patients treated with statins (Athyros and Mikhailidis 2012; Banach et al. 2013; Katsiki et al. 2015). If statins cannot be used or do not achieve guideline targets an alternative therapeutic approach is recommended. This includes other lipid lowering drugs, with the possibilities of combination therapy (Katsiki et al. 2013; Rizzo et al. 2013a) and/or natural compounds present in the human diet (Patti et al. 2015; Serban et al. 2015; Ursoniu et al. 2015).

Abbreviations: ACAT, acyl CoA:cholesterol O-acyltransferase; AMP, adenosine monophosphate; Apo, apolipoprotein; BPF, bergamot-derived polyphenolic fraction; cIMT, carotid intima-media thickness; CK, creatine kinase; CV, cardiovascular; CVD, cardiovascular disease; DPPH, 1,1-diphenyl-2-picrylhydrazyl; HC, hypercholesterolemia; HDL-C, high-density lipoproteins cholesterol; HepG2, human hepatoma cell line; HG, high blood glucose (>110); HMG-CoA, 3-hydroxy-3-methylglutaryl-Co-enzyme A; HMGF, 3-hydroxy-3-methyl-glutaryl flavanones; HT, hypertryglyceridemia; LDL-C, low-density lipoproteins cholesterol; LOX-1, lectin-like oxyLDL receptor-1; MetS, metabolic syndrome; NAFLD, non-alcoholic fatty liver disease; NOD, new-onset diabetes; PK, protein kinase; PPL, postprandial lipemia; sdLDL, small dense LDL; SMCs, smooth muscle cells; TC, total cholesterol; TG, triglycerides; VLDL-C, very low density lipoproteins cholesterol.

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In vitro and *in vivo* studies indicate that *Citrus* juices positively influence lipid metabolism (Gorinstein et al. 2004) and high contents of bioactive compounds of *Citrus* fruits may lead to reduced risk of CV disease (CVD) (Benavente-Garcia and Castillo 2008). Bergamot, the common name of the fruit *Citrus bergamia Risso* (family *Rutaceae*), differs from other *Citrus* fruits because of its composition and the high content of flavonoids (such as neoeriocitrin, neohesperidin, naringin, rutin, neodesmin, rhoifolin and poncirin) (Dugo et al. 2005; Nogata et al. 2006). The beneficial properties of the juice of *C. bergamia* have been investigated in several studies indicating antimicrobial (Sánchez-González et al. 2010), analgesic (Sakurada et al. 2011), anti-inflammatory (Impellizzeri et al. 2014; Trombetta et al. 2010) and glucose and lipid-lowering properties (Mollace et al. 2011).

The purpose of this review was to summarize the current state of knowledge about the effects of bergamot on lipids based on pre-clinical and clinical studies. Both experimental and epidemiological studies suggest that the polyphenols, particularly flavonoids, present in bergamot also exert antioxidant effects that may be related to a hypolipemic effect (Devaraj et al. 2004).

Search strategy: We searched PubMed and Scopus listings for relevant publications up to September 2015 using combinations of the following keywords: “bergamot”, “cardiovascular risk”, “dyslipidemia”, “lipids”, “lipoproteins”, “low density lipoprotein”, “high density lipoprotein”, “lipid-lowering drugs”, “nutraceuticals”, “natural compounds” and “statin”.

Effects of bergamot on lipid metabolism: evidence from pre-clinical studies

As mentioned above, bergamot (*C. bergamia*) possesses a high content flavonoid glycosides in its juice and albedo, such as neoeriocitrin, neohesperidin, naringin, rutin, neodesmin, rhoifolin and poncirin (Dugo et al. 2005; Nogata et al. 2006) and some statin-like compounds (Di Donna et al. 2009). Three flavanones extracted from the bergamot peel, the 3-hydroxy-3-methyl-glutaryl flavanones enriched fraction (HMGF: brutieridin, melitidin and HMG-neoeriocitrin), act like statins, having a behavior similar to simvastatin in a model of hypercholesterolemic rats (Di Donna et al. 2014). Both simvastatin and HMGF exerted beneficial effects on high-density lipoproteins cholesterol (HDL-C)/low-density lipoproteins cholesterol (LDL-C) ratio and decreased levels of total cholesterol (TC; 30% and 20%, respectively; that also was observed in liver TC: 11% and 35%, respectively), TG (32 and 20%, respectively, and for hepatic TG about 18% and 35%, respectively), very low density lipoproteins cholesterol (VLDL-C; 33% and 28%, respectively) and LDL-C levels (24% and 40%, respectively), while HDL-C increased exclusively in the HMGF-treated rats (20%) compared with the untreated group (Di Donna et al. 2014). Such HMGF effects have been confirmed by positive gene regulation in the liver together establishing a promising nutraceutical strategy for the control of hypercholesterolemia, a main factor responsible for increased CVD risk (Di Donna et al. 2014). In addition, naringin, also present in grapefruit, as well as neoeriocitrin and rutin have been reported to be active in animal models of atherosclerosis (Choe et al. 2001) and have been shown to inhibit the oxidation of LDL (Yu et al. 2005), supporting that bergamot may prevent atherosclerosis (Miceli et al. 2007). Briefly, *C. bergamia* has been administered to hyperlipidemic rats (1 ml/rat/day) in order to investigate its protective effect on the liver (Miceli et al. 2007). A significant reduction in serum TC (29.27%), triglycerides (TG; 46.12%), and LDL-C levels (51.72%) and an increase in HDL-C levels (27.61%) were reported. Additionally, it was suggested that such hypocholesterolemic effect of *C. bergamia* may be mediated by the increase in fecal neutral sterols and total bile acids excretion (Miceli et al. 2007).

In addition to the hypolipidemic effect, bergamot showed radical scavenging activity in the rat model, while histopathological observations showed a protective role on hepatic parenchyma (Miceli et al. 2007). Similarly, the protective effect of treatment with bergamot juice (1 ml/day, for 30 days) against hypercholesterolemic diet-induced renal injury in rats has been investigated (Trovato et al. 2010). Plasma levels of TC, TG and LDL-C fell significantly, while HDL-C levels increased. Plasma creatinine levels did not change compared with hyperlipidemic controls. However, bergamot juice administration significantly decreased malondialdehyde levels, a good biomarker of oxidative stress, one of the major aldehydes formed during lipid peroxidation. In addition, the histological observations of the kidney supported the biochemical findings and suggested a protective effect of bergamot juice in the development of renal damage in hypercholesterolemic rats (Trovato et al. 2010). Furthermore, the antioxidant potential of bergamot juice was examined in two *in vitro* systems: in the free radical 1,1-diphenyl-2-picrylhydrazyl (DPPH) assay the juice showed a noticeable effect on scavenging free radicals, and in the reducing power assay it showed a strong activity as well. These findings suggest that a protective role of bergamot in hypercholesterolemic diet-induced renal damage may be attributed to its antioxidant properties (Trovato et al., 2010). These 2 studies (Miceli et al. 2007; Trovato et al. 2010) support the hypolipemic and vasoprotective effects of bergamot and its constituents (flavonoids and pectins) on vascular damage induced by stress that may also lead to reduced CVD risk.

Polyphenols, particularly, flavonoids, such as melitidin and brutieridin in combination with other flavonoid glycosides present in bergamot, are suggested to be responsible for reducing cholesterol levels (Dugo et al. 2005; Nogata et al. 2006). However, the exact mechanism of hypolipidemic activity remains unclear. Leopoldini et al. (Leopoldini et al. 2010) applied the density functional theory to study the mode of binding of the flavonoid conjugates, brutieridin and melitidin, quantified in bergamot fruit extracts, to the active site of HMG-CoA reductase. This was compared with that of simvastatin, in order to obtain better insight into the inhibition process of this key enzyme in sterol biosynthesis. Brutieridin and melitidin were identified to be structural analogues of statins and to partially occupy the site that accepts the part of the CoA substrate, similar to the binding mode of simvastatin (Leopoldini et al. 2010). Consistent with the presence of the HMG-like moiety, brutieridin and melitidin compounds seem to be competitive inhibitors of HMG-CoA reductase with respect to the binding of HMG-CoA. Similarly, our previous study showed that flavonolignans modulate lipid homeostasis by regulating the expression and activity of acyl-CoA oxidase, stearoyl-CoA desaturase 1 and liver-fatty acid binding protein (Salamone et al. 2012).

It has been suggested that both tangerine peel extract and a mixture of two citrus flavonoids, naringin and hesperidin, reduce cholesterol levels by modulating the activities of HMG-CoA reductase and acyl CoA:cholesterol *O*-acyltransferase (ACAT) (Bok et al. 1999). Binding to bile acids and increasing the turnover rate of blood and liver cholesterol were reported as a possible mechanism (Bok et al. 1999). As mentioned above, bergamot improves fecal excretion of sterols in rats (Miceli et al. 2007), suggesting that the hypocholesterolemic effect of bergamot may be mediated by the increase in fecal neutral sterols and total bile acids excretion as well as that the intake of bergamot may reduce the risk of CVD through its radical scavenging function and hypocholesterolemic action.

In vitro studies in human hepatoma cell line (HepG2) have shown that naringenin and hesperetin reduce the availability of lipids for the assembly of apolipoprotein (apo) B-containing lipoproteins, an effect mediated by the reduction of ACAT activity (Wilcox et al. 2001). Lectin-like oxyLDL receptor-1 (LOX-1) is