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Clinical application of bergamot (*Citrus bergamia*) for reducing high cholesterol and cardiovascular disease markers

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Abstract

The bergamot is a citrus fruit native to southern Italy with traditional uses that include improving immune response and cardiovascular function. There are a variety of phytochemicals that have been found in the bergamot including brutieridin and melitidin as well as other flavonoids, flavones O-glucosides and C-glucosides. Multiple clinical trials have provided evidence that different forms of orally administered bergamot can reduce total cholesterol and low-density lipoprotein cholesterol. In vitro mechanistic studies have provided evidence that polyphenols from the bergamot can alter the function of AMPK and pancreatic cholesterol ester hydrolase (pCEH). The use of bergamot in multiple clinical trials has consistently shown that it is well tolerated in studies ranging from 30 days to 12 weeks. This mini-review reports on the clinical studies performed with different forms of bergamot along with their effectiveness in reducing total cholesterol and LDL cholesterol in patients with hypercholesterolemia.

Keywords

Bergamot; brutieridin; melitidin; cholesterol; antioxidant; *Citrus bergamia*

Background

Citrus fruits are rich in flavonoids and have long been associated with improving human health outcomes in areas that include improved immune response, coronary artery disease, heart failure, and high cholesterol. One citrus fruit in particular that has gained attention for improving health outcomes is the bergamot (*Citrus bergamia*) [1]. This fruit is primarily found in Southern Italy in the area known as Calabria with attributes that include antioxidant, anti-inflammatory, and cholesterol reducing functions [2, 3]. In Italian traditional medicine the bergamot has been used to treat or cure a variety of symptoms that include fever, sore throat, mouth and skin infections, and infections of the respiratory system and the urinary tract [1]. Recent studies have validated the anti-microbial properties of bergamot in *in vitro* settings [4, 5, 6].

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Conflicts of Interest

The authors do not declare any conflicts of interest

Dyslipidemia is an important risk factor for the development of atherosclerosis and eventual coronary artery disease. Dyslipidemia is evidenced by increased concentrations (i.e. hyperlipidemia) of low-density lipoprotein cholesterol (LDL-C), total blood cholesterol, and triglycerides. Hyperlipidemia is often accompanied by insulin resistance including impaired glucose tolerance, or “pre-diabetes”, and low levels of high-density lipoprotein cholesterol (HDL-C) [7]. The three most common pharmacological approaches to lowering hypercholesterolemia include bile acid sequestrants, statins, and inhibitors of cholesterol absorption (i.e. ezetimibe). Of these three, the statin family represents the most favored approach as evidenced by current protocols favoring statin use, annual sales of statins, and clinical studies suggesting significant reductions in cardiovascular events, morbidity, and mortality with statins [8]. The primary mechanism of statins includes the inhibition of the enzyme catalyzing the rate-limiting step in mevalonate biosynthesis. This key intermediate in cholesterol metabolism is essential for *de novo* cholesterol synthesis. Along with the inhibition of cholesterol synthesis, there are known dose related side effects shown in estimates as high as 22% of patients utilizing statins, including liver disease or severe myopathy [9, 10]. Given the documented benefits of lowering LDL-C, triglycerides, and total cholesterol, additional dietary and phytochemical approaches should be investigated as alternative methods to reducing indices of hyperlipidemia. One such example includes the bergamot fruit that has been investigated in pre-clinical and clinical studies for improving dysplipidemia.

The tree *Citrus bergamia* belonging to the Rutaceae family is found in the Calabria region specifically, due to its unique climate that is suitable for its growth. Essential oils of the bergamot peel are well characterized and used extensively in products ranging from the food industry, pharmaceutical industry, and the cosmetic industry [1, 11]. Previous studies have suggested that the essential oil contains up to 93–96% volatile phytochemicals that include monoterpenes (25–53%), linalool (2–20%) and linalyl acetate (15–40%). The non-volatile compounds include waxes, pigments, coumarins, and psoralens. The bergamot fruit also contains flavonoids that include neoeriocitrin, naringin and neohesperidin among many others that have been of interest for their cardiovascular benefits. In this review we will evaluate the clinical evidence for bergamot as a strategy for improving dyslipidemia.

Phytochemical constituents of bergamot

Though most citrus fruits are known to contain flavonoids, the bergamot is unique in that it contains an especially high content of flavonoids [12, 13, 14, 15]. Neoeriocitrin, naringin and neohesperidin have all been isolated and identified in bergamot. C-glucoside flavonoids identified in bergamot include apigenin 6,8-di-C-glucoside, diometin 6,8-di-C-glucoside, lucenin-2, vicenin-2, stellarin-2, lucenin-2-40-methyl ether, scoparin, and orientin 40-methyl ether; Flavone O-glycosides identified in bergamot include brutieridin, melitidin, rhoifolin 40-O-glucoside, chrysoeriol 7-O-neohesperidoside-40-O-glucoside, diosmin, rhoifolin, chrysoeriol 7-O-neohesperidoside, narirutin, and neodiosmin. Considering the high content of volatile compounds, it is unsurprising that the bergamot peel and many other citrus peels are widely used in the perfume and cosmetic industries. A study by Mondello et al found that bergamot essential oil contains more than 100 volatile compounds while linalyl acetate and linalool were predominant in addition to limonene [16].

Mechanism of action of phytochemicals from the bergamot

Inhibiting oxidation of LDL particles

Oxidation of low-density lipoprotein particles is a harmful form of cholesterol that results from free radical damage. This form of oxidative damage, along with increased inflammatory events, has been associated with atherosclerosis that ultimately alters cardiovascular blood flow. Several constituents including naringin, neoeriocitrin, and rutin from the bergamot have been reported to lower the oxidation of LDL particles. Studies using naringin, neoeriocitrin and rutin reported them to have antioxidant activity in *in vitro* antioxidant models by beta-carotene-linoleic acid, 1,1-diphenyl-2-picryl hydrazyl (DPPH), superoxide, and hamster low-density lipoprotein (LDL) [17].

In another study, male New Zealand rabbits were fed a high cholesterol diet and divided into three groups as follows: 1) placebo (i.e. control group) 2) naringin and 3) lovastatin [18]. The results revealed that naringin significantly reduced fatty streak formation and macrophage infiltration in endothelial cells. In addition, naringin was found to be hepatoprotective while lovastatin was not found to be hepatoprotective. Naringin-inhibited-cholesterol also induced elevation of intercellular adhesion molecule-1 (ICAM-1) in endothelial cells. ICAM-1 levels have been reported to be elevated in response to normal immune function disruption in endothelial cells leading to atherosclerosis [19].

Reactive oxygen species (ROS) including superoxide (O_2^-), hydrogen peroxide (H_2O_2), and hydroxyl radicals (OH^-) can directly damage cells in the cardiovascular system and induce proinflammatory events. In addition, ROS can induce the formation of peroxynitrite ($ONOO^-$) and is associated with neointima formation. This formation of scar tissue can also result from a balloon angioplasty procedure. An *in vivo* study evaluated the impact of bergamot on injured blood vessels following angioplasty in rats [20]. Pre-treatment of rats with the non-volatile fraction of bergamot reduced free radical formation and Lectin-like oxyLDL receptor-1 (LOX-1). These results show that 14 days of consecutive administration of bergamot oil antagonized the effects of smooth muscle cell proliferation and neointima formation in the rat carotid artery following angioplasty.

Oxidized LDL leads to vasoconstriction mediated by the inflammatory thromboxane A2 [21]. Studies have suggested that glomerular injuries and hemodynamic abnormalities of the kidney may by directly caused by interaction of oxidized LDL with mesangial cells Wheeler et al., 1994. The renal protective properties of bergamot juice were tested in rats receiving a hyperlipidemic diet [22]. Bergamot juice (1 mL) was found to significantly decrease malondialdehyde (MDA) levels compared to hyperlipidemic controls (4.10 ± 0.10 nmol/mg protein and 4.78 ± 0.15 nmol/mg protein, respectively). Biochemical data also reported that histological preparations of the kidney suggests that bergamot juice prevented the development of renal damage from hypercholesterolemia.

Hypolipidemic properties of bergamot polyphenols

HMG-CoA reductase is the rate controlling enzyme in the mevalonate pathway that is responsible for cholesterol synthesis. The class of compounds known as statins are potent inhibitors of HMG-CoA by competitively binding the active site where HMG binds. This

makes HMG-CoA a valuable target for reducing cholesterol levels. A study by Di Donna et al in 2009 proposed two molecules from bergamot, neohesperidin and naringin, as sharing structural similarity to statins [23]. A more recent study by Leopoldini reported through computational modelling that bergamot's statin-like molecules bind to HMG-CoA at Arg590, Ser684, Asp690, Lys692, and Lys735 residues, as well as at the nonpolar amino acids [24]. To date, there has not been any definitive *in vitro* validation that flavonoids from bergamot share a similar mechanism for inhibition of HMG-CoA reductase. Though no clinical trials have reported on the coenzyme Q10 levels following bergamot administration, it may be another possible benefit over statins, as statins are well known to decrease plasma levels of coenzyme Q10 [25].

A second mechanism that has been proposed with bergamot polyphenols is the activation of adenosine monophosphate-activated protein kinase (AMPK). Activation of AMPK by small molecules improves glucose homeostasis, lipid profiles, blood pressure and insulin resistance and is one of the proposed mechanisms of metformin. Naringin was found to promote phosphorylation of AMPK in the liver at threonine-172 in C57BL/6J mice receiving a high fat diet [26]. These results were further confirmed in HepG2 cells that were exposed to naringin. A study by Sui et al revealed that naringin activates AMPK altering the expression of proprotein convertase subtilisin/kexin type 9 (PCSK9), sterol regulatory element-binding proteins (SREBPs), and low-density lipoprotein receptor (LDLR) [27]. The results of this study identified naringin as an AMPK activator in mice, leading to a down-regulated expression of SREBPs and PCSK9, and an increased expression of LDLR to reduce the body weight of obese C57BL/6J mice. A statistically significant decrease in triglycerides, LDL and total cholesterol was observed. Increasing the expression of LDL receptor is beneficial for promoting the endocytosis of cholesterol rich LDL.

In vivo studies have reported that oral administration of bergamot juice can reduce blood cholesterol and improve the atherogenic index in mice. Hand pressed bergamot juice was administered to Wistar rats weighing 180 to 200 grams while being administered a high cholesterol diet [28]. The animal feed included cholesterol, 2%; sodium cholate, 2%; vitamin mixture, 2%; oligoelements, 0.2%; salt mixture, 5.8%; coconut oil, 20%; cellulose, 4%; sucrose, 44%; casein, 5%; drakettprotein, 15%. Animals were divided into three groups as follows: 1) normolipidemic control rats on a standard diet 2) hypercholesterolemic diet for 30 days and 3) hypercholesterolemic diet for 30 days receiving 1 mL of bergamot juice daily for 30 days. The main flavonoids identified in the present study were 1) neoeriocitrin (370 ppm), 2) naringin (520 ppm), and 3) neohesperidin (310 ppm). Bergamot juice was found to reduce cholesterol (29.27%), triglycerides (46.12%), and LDL (51.72%) and an increase in HDL (27.61%) levels versus hypercholesterolemic controls. The atherogenic index was 1.09 ± 0.10 in the C. bergamia-treated group as compared with 3.09 ± 0.20 in the hypercholesterolemic group.

Pancreatic cholesterol ester hydrolase (pCEH) represents an additional target in disrupting cholesterol synthesis. This enzyme catalyzes the hydrolysis of sterol esters into sterols and fatty acids. Disruption of this reaction can significantly improve the serum lipid profile in hyperlipidemic patients. An *in vivo* study identifies the bergamot polyphenol fraction as capable of disrupting pCEH [29]. Male Sprague-Dawley rats (200–225 g) received a normal

diet or a high cholesterol diet. Rats receiving bergamot polyphenol fraction at 10 mg/kg by oral gavage were found to inhibit pCEH activity.

Clinical trials with bergamot for hypercholesterolemia

Mollace (2018)—A randomized double-blind placebo-controlled study evaluated a bergamot polyphenol fraction for lowering hyperlipidemia [30]. Patients were randomized into three groups as follows: 1) placebo (n=20) 2) bergamot polyphenol fraction (n=20) and 3) bergamot polyphenol fraction phytosomal formulation (n=20). Patients were enrolled in the study with mixed hyperlipidemia defined as LDL cholesterol > 120 mg/dl and triglycerides > 175 mg/dl, and serum glucose > 110 mg/dl. Human subjects in the bergamot polyphenol fraction (BPF) group received 650 mg taken twice daily and subjects in the bergamot polyphenol fraction phytosomal formulation group (BPF Phyto) received 500 mg taken twice daily; both were taken for 30 days. The bergamot polyphenol fraction decreased total cholesterol from 262 to 196, LDL cholesterol from 175 to 116, and triglycerides from 252 to 170. Similar results were observed with BPF Phyto: it decreased total cholesterol from 261 to 198, LDL cholesterol from 174 to 113, and triglycerides from 252 to 173. Both formulations were able to show an increase in HDL cholesterol with BPF increasing HDL from 44 to 48 and BPF Phyto from 44 to 50. Decreases in serum glucose were observed with BPF from 120 to 98 and BPF Phyto from 124 to 96. No changes were observed in the placebo group. The results suggest that both formulations were able to significantly modify cholesterol levels after 30 days. A second outcome that was measured included the pharmacokinetics of key flavonoids found in bergamot including naringin, naringenin, and naringenin glucuronide. No significant differences existed between the two different formulations of bergamot in this clinical trial.

Toth (2016)—An open label clinical trial evaluated bergamot derived extract in 80 human subjects (42 men and 38 women, mean age 55 ± 13) with moderate hypercholesterolemia (i.e. 160 −190 mg/dl) [31]. The subjects received 150 mg of bergamot flavonoids (standardized to contain 16% neoeriocitrin, 47% neohesperidin, and 37% naringin) daily for 6 months. Bergamot was observed to decrease total cholesterol from 255 to 224, LDL cholesterol from 159 to 132, and triglycerides from 159 to 133. An increase in HDL was observed with bergamot from 50 to 54. LDL was divided into 7 subclasses that included LDL-1 and LDL-2, representing large LDL, and LDL-3–7 representing atherogenic small, dense LDL. A significant increase in LDL-1 (from 41.2% ± 0.2% to 49.6% ± 0.2%, $p < 0.0001$) was observed. A decrease in the small dense LDL-3, −4, and −5 particles (from 14.5% ± 0.1% to 9.0% ± 0.1% $p < 0.0001$; 3.2% ± 0.1% to 1.5% ± 0.1% $p = 0.0053$; 0.3% ± 0.0% to 0.1% ± 0.0% $p = 0.0133$, respectively). Bergamot decreased cIMT from 1.2 mm ± 0.4 to 0.9 mm ± 0.1 ($p < 0.0001$).

Babish (2016)—An observational, one-arm study was conducted with 11 human participants (3 male and 8 female; age 38–65 years) and evaluated a combination of 9 plant extracts that included bergamot fruit extract [32]. The extract (i.e. F105) was formulated with apple fruit extract, bergamot fruit extract, blueberry fruit concentrate, capsicum fruit, grape seed extract, grape skin extract, green tea leaf extract, mangosteen pericarp extract, olive leaf extract, and turmeric root & rhizome extract in a number of ratios beginning with

8.5%, 70.4%, 1.4%, 1.4%, 1.4%, 1.4%, 4.2%, 1.4%, 1.4%, and 8.5% representing F105, respectively. Patients were directed to take 2 capsules daily (total 500 mg of bergamot fruit extract and 220 mg phytochemical complex blend) for 12 weeks. A reduction of total cholesterol (7.3%), LDL cholesterol (10%), and apolipoprotein B (2.8%) was observed. Changes in levels of lipoprotein(a), triglycerides, and HDL were observed, however, they were not statistically significant. Additionally, one patient who was non-responsive to statin therapy (20 mg) was enrolled and was directed to take 720 mg of F105 for the duration of the study during the evening meal. After 12 weeks, a reduction compared to baseline was observed with LDL (−8%), total cholesterol (−4%), triglycerides (−34%), oxidized LDL (−6%) and an increase in HDL (54%) occurred. Clinical observations of this study suggest the F105 extract was safe and efficacious in lowering of lipid biomarkers.

Gliozzi (2013)—A prospective, open-label, parallel group, placebo-controlled study with 77 human subjects with elevated LDL and triglycerides were administered 1) placebo (n=15) 2) rosuvastatin 10 mg (n=16) 3) rosuvastatin 20 mg (n=16) 4) bergamot polyphenol fraction (BPF) (n=15) or 5) bergamot polyphenol fraction with rosuvastatin (n=15) [33]. The total duration of the study was 30 days. Capsules containing 500 mg of bergamot polyphenol fraction with 50 mg of ascorbic acid were encapsulated for the study. The principle flavonoids in the bergamot polyphenol fraction were neoeriocitrin, naringin, and neohesperidin. Both doses of rosuvastatin and BPF reduced total cholesterol, LDL, and urinary mevalonate. The results of this study suggest a combination of rosuvastatin and BPF were safe when taken together for 30 days. Further research beyond 30 days would be needed to determine if rosuvastatin and BPF can safely continue to be taken in combination.

Mollace (2011)—A randomized, double-blind, placebo-controlled clinical trial evaluated bergamot (500 mg or 1,000 mg per day) for three months to reduce total cholesterol, reduce LDL, and increase HDL [34]. A total of 237 human subjects were enrolled in the study. Total cholesterol was reduced by 20% (500 mg of bergamot) and 30.9% (1,000 mg of bergamot). LDL was reduced by 23% (500 mg bergamot) and by 38.6% (1,000 mg of bergamot). HDL was increased by 25.9% (500 mg of bergamot) and by 39% (1,000 mg of bergamot). In 6 patients treated daily with 500 mg and in 11 patients taking 1000 mg of BPF, a moderate gastric pyrosis was observed. However, none of the patients taking BPF interrupted the treatment. Interestingly, this study enrolled 32 human subjects who experienced statin toxicity. Prior to their enrollment to the bergamot study, human subjects stopped taking statins for 2 months. They were then administered 1500 mg of BPF daily. After 30 days, those patients receiving BPF had changes in total cholesterol (−25%) and LDL (−27.6%) without reappearance of statin toxicity. Taken together, the results of this study suggest that BPF can reduce total cholesterol, LDL, and triglycerides.

Conclusion

The results of five different clinical trials (Table 1) using bergamot in various forms suggest the polyphenol fraction can lower LDL-C and total cholesterol. Several studies suggested that bergamot polyphenols can reduce triglycerides and increase HDL-C, however, the results were not consistent across all studies. One possible explanation for this variability (i.e. TG and HDL-C) is that bergamot preparation, extraction, and standardization varied in

several studies. Consistently in all of the clinical trials bergamot appeared to be well tolerated with studies ranging from 30 days to 6 months. There are several weaknesses in the design of several of the clinical trials that used an open label design (Table 1). However, it should be noted that each patient can serve as their own control since cholesterol was quantified prior to bergamot and at the completion of the study. Three of the studies suggested an increase in HDL by up to 4 mg/dl (Table 1). This is significant because HDL is often difficult to increase apart from lifestyle changes. Regarding the mechanism of action there are several possible mechanisms that may be responsible for improving cholesterol lab values including activation of AMPK and inhibition of pancreatic cholesterol ester hydrolase (pCEH). As of now the suggestions that bergamot inhibits HMG-CoA reductase appear to be largely based on molecular modeling and will require further studies to confirm this proposed mechanism of action. Taken together, these early clinical trials along with the mechanistic studies that have been performed suggest that bergamot can reduce total cholesterol and LDL-C through mechanisms that are distinct from current pharmaceutical approaches.

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Table 1.

Summary of clinical trials using bergamot for hypercholesterolemia

Authors and Year	Study Design	Study Agent(s)	Human Subjects	Results
Mollace (2018)	Randomized, double blind, placebo-controlled Site: Catanzaro, Italy	1. 650 mg tablet twice daily of Bergamot Polyphenol Fraction (BPF; 38% polyphenols) 2. 500 mg tablet twice daily of BPF Phytosome (*each table equivalent to 200 mg of BPF extract) 3. Placebo tablets had no active ingredient Study agents were taken 30 minutes before meals two times daily	60 (n=20 received BPF, n=20 received BPF Phyto and n=20 received placebo) Inclusion criteria: >120 mg/dL LDL-C >175 mg/dL Triglycerides >110 mg/dL serum glucose	Total Cholesterol BPF Day 0: 262 ± 14 Day 30: 196 ± 12 BPF Phyto Day 0: 261 ± 16 Day 30: 198 ± 13 LDL-C BPF Day 0: 175.8 ± 5.8 Day 30: 116 ± 3.2 BPF Phyto Day 0: 174 ± 5.7 Day 30: 113 ± 3.8 Triglycerides BPF Day 0: 252 ± 9 Day 30: 170 ± 7 BPF Phyto Day 0: 252 ± 8 Day 30: 173 ± 6 HDL-C BPF Day 0: 44 ± 4.1 Day 30: 48 ± 3.8 BPF Phyto Day 0: 44 ± 4.4 Day 30: 50 ± 4.2 Glucose BPF Day 0: 120 ± 1.6 Day 30: 98 ± 1.3 BPF Phyto Day 0: 124 ± 1.5 Day 30: 96 ± 1.4
Toth (2016)	Open-label, one-arm Site: Palermo, Italy	Bergavit R® (a Bergamot juice derived extract containing 150 mg flavonoids) was given daily at a fixed dose for 6 months	80 (42 men, 38 women) Inclusion criteria: 160–190 mg/dL LDL-C Must not have severe renal or hepatic diseases	Total Cholesterol Day 0: 257 ± 15 6 months: 223 ± 41 HDL-C Day 0: 48 ± 10 6 months: 52 ± 14 Triglycerides Day 0: 162 ± 54 6 months: 136 ± 79 LDL-C Day 0: 176 ± 8 6 months: 144 ± 37
Babish (2016)	Open-label, one-arm Site: California, USA	2 capsules of F105 (total 500 mg bergamot fruit extract and 220 mg phytocomplex blend) were taken daily at dinnertime for 12 weeks	11 (3 men, 8 women) Inclusion criteria: 18–40 kg/m^2 BMI 150–350 mg/dL LDL-C 150–400 mg/dL Triglycerides	Cholesterol Day 0: 248 (191–286) 12 weeks: 228 (197–266) LDL-C Day 0: 162 (123–220) 12 weeks: 143 (112–199) Triglycerides Day 0: 186 (118–473) 12 weeks: 207 (86–260) HDL-C Day 0: 42 (22–76) 12 weeks: 42 (26–68) Non-HDL-C Day 0: 214 (173–250) 12 weeks: 222 (152–242) Glucose Day 0: 94 (82–228) 12 weeks: 93 (78–206)

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Gliozzi (2013)	Open-label, parallel group, placebo-controlled Site: Rome, Italy	1. Placebo tablet had no active ingredient 2. 10 mg Rosuvastatin 3. 20 mg Rosuvastatin 4. 1000 mg BPF (+ 50 mg ascorbic acid) 5. 1000 mg BPF (+50 mg ascorbic acid) + 10 mg Rosuvastatin Study agents were taken before meals, once daily for 30 days	77 (n=15 received placebo, n=16 received low Rosuvastatin, n=16 received high Rosuvastatin, n=15 received BPF, n=15 received BPF + Rosuvastatin) Inclusion criteria: >160 mg/dL LDL-C >225 mg/dL Triglycerides	Initial measurements were averaged from all patients. Cholesterol Day 0: 278 ± 4 Low Rosuvastatin Day 30: 195 ± 3 High Rosuvastatin Day 30: 174 ± 4 BPF Day 30: 191 ± 5 BPF + Rosuvastatin Day 30: 172 ± 3 LDL-C Day 0: 191 ± 3 Low Rosuvastatin Day 30: 115 ± 4 High Rosuvastatin Day 30: 87 ± 3 BPF Day 30: 113 ± 4 BPF + Rosuvastatin Day 30: 90 ± 4 HDL-C Day 0: 38 ± 2 Low Rosuvastatin Day 30: 42 ± 3 High Rosuvastatin Day 30: 48 ± 3 BPF group Day 30: 45 ± 4 BPF + Rosuvastatin Day 30: 52 ± 4 Triglycerides Day 0: 238 ± 5 Low Rosuvastatin Day 30: 200 ± 4 High Rosuvastatin Day 30: 202 ± 5 BPF Day 30: 165 ± 3 BPF + Rosuvastatin Day 30: 152 ± 5
Mollace (2011)	Randomized, double blind, placebo-controlled Site: Rome and Marinella di Bruzzano, Italy	1. 500 mg BPF (+50 mg ascorbic acid) 2. 1000 mg BPF (+50 mg ascorbic acid) 3. Placebo tablet had no active ingredients 4.For Group D only***– 1500 mg BPF Study agents were taken before meals, once daily, for 30 days	237 Group A – Hypercholesterolemia, n=104 >130 mg/dL LDL-C Group B – Hypercholesterolemia + hypertriglyceridemia, n=42 Group C – Hypercholesterolemia + hypertriglyceridemia + hyperglycemia, n=59 >110 mg/dL Glucose Group D – patients who stopped simvastatin treatment due to muscular pain or significant elevation of creatine-phospho-kinase, n=32 Each group (excluding Group D) was split into three smaller groups which each received one of the study agents	Results presented in % Δ ± SEM; mean values for cohorts were not provided. Values represent mean change. Cholesterol A low: −20.7 ± 1 A high: −30.9 ± 1.5 A placebo: −0.4 ± 0.4 B low: −21.9 ± 1.8 B high: −27.7 ± 3.4 B placebo: −0.5 ± 0.5 C low: −24.7 ± 2.6 C high: −28.1 ± 2.6 C placebo: 0.5 ± 0.5 D: −25.0 ± 1.6 LDL-C A low: −23.0 ± 1.9 A high: −38.6 ± 1.5 A placebo: −1.7 ± 0.5 B low: −25.3 ± 2.0 B high: −33.4 ± 3.9 B placebo: −0.5 ± 0.7 C low: −26.8 ± 3.6 C high: −33.2 ± 3.0 C placebo: −0.9 ± 1.4 D: −27.6 ± 0.5 HDL-C A low: 25.9 ± 2.3 A high: 39.0 ± 2.8 A placebo: 0.5 ± 1.1 B low: 17.3 ± 1.4 B high: 35.8 ± 4.2

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				B placebo: −1.3 ± 1.8 C low: 16.5 ± 1.6 C high: 29.6 ± 1.8 C placebo: 2.9 ± 2.0 D: 23.8 ± 1.7 <u>Tryglycerides</u> B low: −28.2 ± 3.9 B high: −37.9 ± 3.3 B placebo: 0.1 ± 0.5 C low: −32.7 ± 2.5 C high: −41.0 ± 2.6 C placebo: 0.1 ± 0.5 <u>Glucose</u> C low: −18.9 ± 1.2 C high: −22.4 ± 1.0 C placebo: −0.5 ± 0.7