Comparative effect of a nutraceutical compound based on a flavonoid complex from bergamot on plasma lipids, glucose metabolism and liver enzymes: a 3-arm, double-blind, placebo-controlled, randomized, clinical trial.

Keywords
metabolic syndrome, cardiovascular risk, cholesterol, flavonoids, nutraceuticals, bergamot, prickly pear, Opuntia ficus indica

Abstract
Introduction
Bergamot and opuntia (prickly pear cladodes) standardized extracts have demonstrated to have positive metabolic effects in preclinical and clinical model.

Material and methods
The aim of this study was to evaluate the metabolic effect of a combined nutraceutical containing 150 mg of Opuntia ficus indica extract, 400 mg of Plant sterols, 12.5 mg of Thiamine and 200 mg of Brumex®, a phytocomplex from bergamot fruit (Citrus bergamia Risso et Poiteau, fructus) standardized 40% in total flavonoids and min 5% in 3-hydroxy-3-methylglutaryl-flavanones. Thus, we carried out a randomized, double-blind, placebo-controlled clinical trial on 75 hypercholesterolemic subjects randomized to take the active compound (2 tablets per day), placebo (2 tablets/day), both (1 per product/day).

Results
After 12 weeks of treatment with 1 tablet per day, we observed a significant reduction of a number of metabolic parameters: Total (TC)= -14.6%, low-density lipoprotein (LDL-C)= -19.9%, and non high-density lipoprotein cholesterol (non-HDL-C)= -22.1%, triglycerides (TG)= -13.1%, Apolipoprotein B= -16% (all p<0.05 both versus baseline and versus placebo), fasting plasma glucose= -5.1%, glutamate oxaloacetate transaminase= -7.8%, glutamate pyruvate transaminase= -7.3% and gamma-glutamyl transferase= -34.4% (all p<0.05 versus baseline). High-density lipoprotein cholesterol (HDL-C) was increased 6.9% by the use of 1 tablet per day (p<0.05 versus baseline). All parameters were reduced at the same extent when taking the full dose (2 tablets), beyond TG.

Conclusions
The tested nutraceutical compound based on a flavonoid complex from bergamot and opuntia showed a short-term positive impact on plasma lipids, plasma glucose and liver enzyme in overall healthy subjects affected by hypercholesterolemia with low cardiovascular risk.
Comparative effect of a nutraceutical compound based on a flavonoid complex from bergamot on plasma lipids, glucose metabolism and liver enzymes: a 3-arm, double-blind, placebo-controlled, randomized, clinical trial.

Federica Fogacci, Valentina Di Micoli, Maddalena Veronesi, Arrigo F.G. Cicero

1 Hypertension and Cardiovascular risk factors Research Center, Medical and Surgical Sciences Dept., Alma Mater Studiorum University of Bologna, Bologna, Italy.

Corresponding author:
Arrigo F.G. Cicero, MD, PhD
Atherosclerosis and Hypertension Research Group
Medical and Surgical Sciences Department
Sant’Orsola-Malpighi University Hospital
U.O. Medicina Interna Borghi - Via Albertoni, 15
40138 Bologna - Italy
Tel.: ++39 512142224 - Fax: ++39 51391320
E-mail: arrigo.cicero@unibo.it
Abstract

Introduction: Bergamot and opuntia (prickly pear cladodes) standardized extracts have demonstrated to have positive metabolic effects in preclinical and clinical model. Materials and Methods: The aim of this study was to evaluate the metabolic effect of a combined nutraceutical containing 150 mg of *Opuntia ficus Indica* extract, 400 mg of Plant sterols, 12.5 mg of Thiamine and 200 mg of Brumex® a phytocomplex from bergamot fruit (*Citrus bergamia* Risso et Poiteau, fructus) standardized 40% in total flavonoids and min 5% in 3-hydroxy-3-methylglutaryl-flavanones. Thus, we carried out a randomized, double-blind, placebo-controlled clinical trial on 75 hypercholesterolemic subjects randomized to take the active compound (2 tablets per day), placebo (2 tablets per day), both (1 per product per day).

Results: After 12 weeks of treatment with 1 tablet per day, we observed a significant reduction of a number of metabolic parameters: Total cholesterol (TC) = -14.6%, low-density lipoprotein cholesterol (LDL-C) = -19.9%, non high-density lipoprotein cholesterol (non-HDL-C) = -22.1%, triglycerides (TG) = -13.1%, Apolipoprotein B = -16% (all p<0.05 both versus baseline and versus placebo), fasting plasma glucose = -5.1%, glutamate oxaloacetate transaminase = -7.8%, glutamate pyruvate transaminase = -7.3% and gamma-glutamyl transferase = -34.4% (all p<0.05 versus baseline). High-density lipoprotein cholesterol (HDL-C) was increased 6.9% by the use of 1 tablet per day (p<0.05 versus baseline). All parameters were reduced at the same extent when taking the full dose (2 tablets), beyond TG.

Conclusion: the tested nutraceutical compound based on a flavonoid complex from bergamot and opuntia showed a short-term positive impact on plasma lipids, fasting plasma glucose and liver enzyme in overall healthy subjects affected by hypercholesterolemia with low cardiovascular risk.

Key words: *Opuntia ficus* indica, prickly pear, bergamot, metabolic syndrome, flavonoids, cardiovascular risk, cholesterol, nutraceuticals
**Introduction**

Polyphenols are secondary plant metabolites and bioactive compounds naturally occurring in plants, plant-derived products and fungi [1].

During the last decades, the potential beneficial effects of flavonoids, especially on the human cardiovascular health, has caught the attention of researchers across the world. Indeed, flavonoids are able to decrease the oxidation of low-density lipoproteins. Furthermore, flavonoids positively impact on the cardiovascular system, thanks to their ability to produce vasodilation and regulate apoptotic processes in the endothelium. It seems that the great antioxidant properties of flavonoids drive all these effects, along with their anti-inflammatory function; however, recently, different mechanisms involved in the beneficial effect of flavonoids on the human body have been identified, showing multiple signaling pathways related to them [2]. Some of them have also been associated to improvement of symptoms in heart failure patients [3].

Pooling data from several epidemiological and clinical studies, total flavonoids and specific subclasses have been associated with a reduced incidence of cardiovascular diseases (CVD), diabetes mellitus and all-cause mortality [4].

Flavonoids have been shown to act as free radical scavenging, and exert antioxidant, hepatoprotective and anti-inflammatory activities [5]. Actually, flavonoids’ biological activities reflect their chemical and biochemical properties, including the ability to regulate the gene expression in chronic diseases and modulate several molecular pathways [6].

Recently, bergamot and opuntia standardized extracts have been suggested as safe natural compounds able to modify some components of the metabolic syndrome [7,8]. In particular, *Citrus bergamia* Risso, a citrus fruit native to southern Italy, known as bergamot, with uses including the improvement of immune response and cardiovascular function, has shown a significant degree of hypocholesterolemic and antioxidant activity. It also has a particular flavonoid composition, as it contains some flavanones that may act as natural statins. Multiple clinical studies have provided
evidence that different forms of orally administered bergamot can reduce total cholesterol and low-density lipoprotein cholesterol [9,10].

At the same time, over the past decade, academic scientists and private companies have provided compelling evidence of *Opuntia ficus Indica*’s potential. Due to its rich composition in polyphenols, vitamins, polyunsaturated fatty acids and amino acids it has been shown to possess anti-inflammatory, antioxidant, hypoglycemic, antimicrobial and neuroprotective properties [11]. The hypoglycemic properties seem to be related to the fibrous component (soluble fibers), such as pectins and mucilages, which exert a mechanical effect on the binding of sugars taken with the diet, thus reducing their absorption, and increasing the fecal excretion. Its cholesterol-lowering properties may be ascribed to a metabolic action, linked to the cholesterol pathways (Figure 1). This can be exerted partly by the pectin component and partly to the polyphenolic component, also responsible for the antiatherogenic activity.[10,12]

In this context, we could suppose that a combined dietary supplement rich in polyphenols and fibers derived from the Mediterranean fruits could have a global positive impact on human metabolism.

Then, we aimed to evaluate if dietary supplementation with a nutraceutical compound containing bergamot and opuntia extracts could positively affect serum lipids concentration, glucose metabolism, and liver parameters in healthy hypercholesterolemic subjects with low estimated cardiovascular risk.

**Materials and methods**

We carried out a three parallel arms, double blind, placebo-controlled, randomized clinical trial in 75 hypercholesterolemic subjects in primary prevention and low estimated risk for cardiovascular diseases.

The study was fully conducted in accordance with the Declaration of Helsinki, its protocol was approved by the Ethical Committee of the University of Bologna, and informed consent was obtained from all patients before the inclusion in the study. Inclusion criteria were age between 18 and 70
years, and LDL-Cholesterol level between 115 and 190 mg/dL, confirmed in at least two sequential checks before signing the consent form.

Enrolled patients were age- and sex- matched and were consecutively enrolled in the outpatient service of cardiovascular disease prevention of the Medical and Surgical Sciences Department of University of Bologna.

Exclusion criteria were:

- Personal history of cardiovascular disease nor risk equivalents
- Smoking habit
- TG>400 mg/dL and/or HDL-C<35 mg/dL
- Obesity (BMI>30 kg/m²)
- Assumption of lipid-lowering drugs or drugs affecting lipid metabolism
- Known thyroid, liver, renal or muscle diseases

At baseline, patients were given standard behavioral and qualitative (not quantitative) dietary suggestions to correct unhealthy habits. Standard diet advice was given by a dietitian and/or specialist doctor. Dietitian and/or specialist doctor periodically provided instruction on dietary intake recording procedures as part of a behavior modification program and then later used the subject’s food diaries for counseling. In particular subjects were instructed to follow general indication of a Mediterranean diet, avoiding excessive intake of dairy products and red meat derived products during the study, maintaining overall constant dietary habits. Individuals were also encouraged to increase their physical activity by walking briskly for 20 to 30 minutes, 3 to 5 times per week, or by cycling.

Treatments

After 2 weeks of diet and physical activity, patients were allocated to treatment with indistinguishable tablets containing placebo or low dose active or high dose active, in 3 groups defined as:

- AA (25 subjects were given two A boxes), AB (25 subjects were given one A and one B box), BB (25 subjects were given two B boxes). A contained a nutraceutical composition (Verum) of 150 mg
of Opuntia ficus Indica extract (75% pectins and mucilages, 3.7% polyphenols), 400 mg of Plant sterols, 12.5 mg of Thiamine and 200 mg of Brumex® a phytocomplex from bergamot fruit (Citrus bergamia Risso et Poiteau, fructus) standardized min 40% total flavonoids and min 5% in HMG (3-hydroxy-3-methylglutaryl-) flavanones, B contained placebo (microcrystalline cellulose, magnesium stearate, silicon dioxide, yellow iron oxide dye, chlorophylline dye, coating agents).

Each subject was instructed to take one tablet from each box assigned at evening, before sleeping.

The treatment has then continued for 12 weeks. Clinical and laboratory data have been obtained at the baseline, and at the end of the trial. Randomization was done using a drawing of envelopes containing randomization codes prepared by an independent statistician through the use of a specific software. The envelopes were then further mixed and distributed to the investigators who assigned the randomization code in a progressive way to the enrolled subjects. A copy of the code was provided only to the person responsible of performing the statistical analysis.

Patients were advised to take the first dose on the day after they were given the study product in a blinded box. At the same time, all unused products were retrieved for inventory. Product compliance was assessed by counting the number of product doses returned at the time of specified clinic visits.

Assessments

Body weight, waist circumference and blood pressure were measured at each visit.

All plasma parameters were obtained after a 12-hour overnight fasting. Venous blood samples were drawn by a nurse in all patients between 8:00 a.m. and 9:00 a.m. Plasma used was obtained by addition of Na$_2$EDTA (1 mL) and centrifuged at 3,000 g for 15 minutes at 48°C. Immediately after centrifugation plasma samples were frozen and stored at -80°C for no more than 3 months. The following parameters were evaluated via standardized methods: [13,14] total cholesterol (TC), high-density lipoprotein-cholesterol (HDL-C), triglycerides (Tg), LDL-Cholesterol (LDL-C), apolipoprotein AI (apoAI), apolipoprotein B100 (apoB), fasting plasma glucose (FPG), glutamate oxaloacetate transaminase (GOT), glutamate pyruvate transaminase (GPT), liver transaminases, gamma-glutamyl-transferase (gGT) and Creatine-Phospho-Kinase (CPK). All measurements were
performed by trained personnel in the Lipid Clinic laboratory of the Medicine and Surgery Sciences Department.

2.4 Statistical analysis

Data have been analyzed using intention to treat by mean of the Statistical Package for Social Science (SPSS) 25.0, version for Windows. The sample size suggested to detect a mean difference of 5% between treatments in term of LDL-reduction, with a power of 0.90 and an alpha error of 0.05, was of at least 20 subjects per group. As per protocol, we decided a priori to check the efficacy of treatments in subjects assuming at least the 90% of the tested products doses foreseen by the trial design. Normally distributed baseline characteristics of the population have been compared using Student’s t test and chi-square test followed by Fisher’s exact test for categorical variables. Between group difference was assessed by the ANOVA followed by the Tukey’s post-hoc test. Inferential analyses have exploratively repeated by gender. All data are expressed as means and SD. A p level of <0.05 was considered significant for all tests.

Results

The baseline characteristics of patients assigned to the different treatment group (25 per group) were similar, and no significant differences were observed regarding the studied parameters (Table 1 and 2). Men and women were equally distribute among groups: 13:12 (placebo), 12:13 (low-dosed verum), 11:14 (full-dosed verum).

Body weight and BMI significantly decreased versus baseline in the full-dosed nutraceutical treated group (p<0.05). No significant change has been detected during the study in all three treatment groups as regards blood pressure (for all, p>0.05) (Table 1).

From the randomization visit to the end of the study, the enrolled subjects maintained overall a similar dietary pattern, without significant change in total energy, total cholesterol and total saturated fatty acid intake. We observed that the low dose of the tested product significantly reduced a number of
metabolic parameters versus baseline: TC = -14.6%, LDL-C = -19.9%, non-HDL-C = -22.1%, TG = -13.1%, ApoB = -16% (all p<0.05 both versus baseline and versus placebo), FPG = -5.1%, GOT = -7.8, GPT = -7.3% and gGT = -34.4% (all p<0.05 versus baseline). HDL was increased 6.9% by the use of 1 tablet per day (p<0.05 versus baseline). All parameters were reduced at the same extent when taking the full dose (2 tablets). However, the full dose showed a better impact on TG (-20.8%) and HDL (13.6%) (all p<0.05 versus baseline) [Table 2].

The placebo group experienced a significant reduction in TG versus baseline, only (p<0.05), as a marker of attention to the suggested diet [Table 2].

The group treated with a single daily dose of the tested nutraceutical compound experienced a significant improvement in the level of all the lipid fractions and lipoproteins levels compared to placebo (p<0.05), but not of liver parameters (p>0.05) [Table 2].

The exploratory repetition of the inferential statistics by gender did not show any significant difference in the observed metabolic changes in men and women.

**Discussion**

A healthy lifestyle remains the cornerstone of cardiometabolic disease prevention [15]. However, during the last decades a large attention has been given to nutraceutical compounds able to improve LDL-C [7,16] level and metabolic syndrome components [6,17]. Among them, polyphenols are particularly of interest for their pleiotropic effect on metabolism and vascular health.[18] However, further clinical data are always required to find most effective products.

In our double-bind, placebo-controlled clinical trial, the groups treated with both a single or a double dose of the tested nutraceutical compound experienced a significant decrease in TC, LDL-C, non-HDL-C, TG, ApoB, FPG, GOT, GPT and gGT, while a significant increase of HDL-C and ApoAI plasma level was seen after 12 weeks of treatment. The results are in agreement with previous literature showing that, in humans, the extract derived from bergamot exerts positive effects on hyperlipidemia demonstrating an effect in the modulation of total cholesterol, triglycerides and LDL.
In particular, bergamot polyphenolic fraction has been demonstrated to improve lipid metabolism by different mechanisms of action: inhibition of 3-hydroxy-3-Methyl-Glutaryl Coenzyme A reductase (naringine, brutieridin and melitidin), modulation of expression and activity of acyl-CoA oxidase, stearoyl-CoA desaturase 1 and liver-fatty acid binding protein (Flavolignans), inhibition of acyl-CoA:cholesterol O-acyltransferase (naringine, hesperidine), binding of biliary salts and improving fecal excretion of sterols.\[20\] However, the results observed in the current study might be due to the concomitant action of bergamot flavonoids and opuntia pectins and mucilages on the lipid levels. Opuntia mucillages and pecting could also improve glucose and lipid pattern, by slowing and partly inhibiting the absorption of food carbohydrates, sterols and lipids in the bowel.\[21\] Moreover, we already showed that Opuntia was able to improve plasma lipid level and atheromasic LDL subfractions in overall healthy subjects \[22\] and in individuals with metabolic syndrome and type 2 diabetes, with significant action in reducing TC and LDL \[23\]. Finally, phytosterols have shown also \[24\] that improve the excretion of cholesterol and the reduction of LDL, mainly competing with dietary and biliary cholesterol absorption in the bowel.\[24\] Supplementation of phytosterol can be of relevant importance in case of diet with a low basal content of phytosterols, as in some cases in the Western diet. All together, these mechanisms of actions could justify the final effect of the tested dietary supplement on plasma lipid level.

The observed improvement in FPG and liver enzyme was also expected. In particular, in a previous double-blind, randomized clinical trial carried out with the same bergamot extract tested in this study, we observed a significant improvement in plasma lipid levels, insulin-resistance, leptin, leptin/adiponectin ratio, high sensitivity-C Reactive Protein, and Tumor Necrosis Factor-α plasma level. \[25\] By the way, the potential antiinflammatory effect of some nutraceuticals and its implication of cardiovascular disease prevention has been recently highlighted by a large expert panel.\[26\]

Given the need of a long-term intake, nutraceutical safety is also of growing interest \[27\]. Overall, the middle-term tolerability components of the tested combined nutraceuticals has been largely
confirmed by the available literature and by our trial, as well. Longer studies are needed to further confirm this observation on the tested nutraceutical combination.

We have to acknowledge some study limitation. In particular, the trial was short so that we cannot infer a longer intake of the tested dietary supplement could have led to eventual further improvement of the studied parameters or to reduction of the positive effect observed. Moreover, the sample size of the study was relatively small, even if adequately powered for the aim of the trial. For the same reason, no advanced statistics has been carried out (namely regression to individuate predictor of better or worse answer to the tested product). As a consequence, one more time, further long-term data on a larger patient sample should be obtained in a new double-blind randomized clinical trial in order to confirm (or less) our current observations.

However, based on our preliminary data, we suggest that synergy between *Citrus bergamia* polyphenols and Opuntia Ficus extracts could be an effective option to expand the therapeutic role in dyslipidemic patients.

In general, the tested product combined with an improvement in life-style could be considered for the management of mildly dyslipidaemic subjects with low-added cardiovascular risk.[28] The lack of statin-like compounds in the tested product will also support the hypothesis of using it in statin-intolerant patients at low-added cardiovascular risk, maybe in association with ezetimibe, as well.[29]

Conclusions

The tested nutraceutical compound based on a flavonoid complex from bergamot and opuntia showed a short-term positive impact on plasma lipids, fasting plasma glucose and liver enzyme in overall healthy subjects affected by hypercholesterolemia and low-added cardiovascular disease risk. Further long-term studies are expected to confirm the metabolic benefit of bergamot polyphenols in combination with Opuntia *Ficus indica* extracts.
Figure 1 – Possible metabolic effect of bergamot and opuntia polyphenols in humans (continuous lines = main action, dot line = minor effects)

HMGGoA = β-Hydroxy β-methylglutaryl-Coenzyme A; NC1L1 = Niemann-Pick C1-Like 1; AMP = 5’ adenosine monophosphate-activated protein
Table 1 – Age, anthropometric and haemodynamic characteristics of the enrolled subjects under different treatment regimen at different study timepoints

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>T1</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre-run-in Placebo Verum Low dose Verum Full dose Placebo Verum Low dose Verum Full dose</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>52±5</td>
<td>54±4</td>
</tr>
<tr>
<td>BW (kg)</td>
<td>63±4</td>
<td>64±5</td>
</tr>
<tr>
<td>WC (cm)</td>
<td>88±6</td>
<td>90.4±4.4</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>22.8±2.2</td>
<td>23.7±1.7</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>134±5</td>
<td>136±5</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>87±2</td>
<td>88±3</td>
</tr>
</tbody>
</table>

*p<0.05 vs. baseline

BW= Body Weight; WC= Waist circumference, BMI= Body Mass Index, SBP= Systolic Blood Pressure, DBP= Diastolic Blood Pressure
Table 2 – Effect of different nutraceuticals regimens on investigated laboratory parameters

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>T1</th>
<th>Placebo</th>
<th>Verum Low dose</th>
<th>Placebo</th>
<th>Verum Low dose</th>
<th>Verum Full dose</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre-run-in</td>
<td>Placebo</td>
<td>Verum Low dose</td>
<td>Verum Full dose</td>
<td>Verum Low dose</td>
<td>Verum Full dose</td>
<td></td>
</tr>
<tr>
<td>TC (mg/dL)</td>
<td>248±13.0</td>
<td>239.8±11.7</td>
<td>246±7</td>
<td>238±13</td>
<td>241±13</td>
<td>210±12°</td>
<td>205±13°</td>
</tr>
<tr>
<td>HDL-C (mg/dL)</td>
<td>44±3</td>
<td>46.5±3</td>
<td>46±2</td>
<td>44±3</td>
<td>44±3</td>
<td>49±1°</td>
<td>50±2°</td>
</tr>
<tr>
<td>LDL-C (mg/dL)</td>
<td>161±8</td>
<td>150.7±10</td>
<td>159±6</td>
<td>155±8</td>
<td>157±9</td>
<td>127±9°</td>
<td>125±8°</td>
</tr>
<tr>
<td>Non HDL-C (mg/dL)</td>
<td>204±11</td>
<td>197.4±10</td>
<td>207±8</td>
<td>198±11</td>
<td>197±12</td>
<td>161±11°</td>
<td>155±12°</td>
</tr>
<tr>
<td>TG (mg/dL)</td>
<td>216±19</td>
<td>205.4±14</td>
<td>195±23</td>
<td>197±16</td>
<td>198±18*</td>
<td>170±16°</td>
<td>156±12°</td>
</tr>
<tr>
<td>ApoB (mg/dL)</td>
<td>146±9</td>
<td>140.1±8</td>
<td>143±7</td>
<td>143±7</td>
<td>141±7</td>
<td>120±9°</td>
<td>119±9°</td>
</tr>
<tr>
<td>ApoAI (mg/dL)</td>
<td>118±12</td>
<td>101.9±12</td>
<td>113±14</td>
<td>114±16</td>
<td>118±14</td>
<td>137±13°</td>
<td>139±11°</td>
</tr>
<tr>
<td>FPG (mg/dL)</td>
<td>88±3</td>
<td>89.5±3</td>
<td>89±3</td>
<td>90±3</td>
<td>88±3</td>
<td>84±2°</td>
<td>83±4°</td>
</tr>
<tr>
<td>GOT (U/L)</td>
<td>23±3</td>
<td>24.5±3</td>
<td>24±2</td>
<td>25±4</td>
<td>25±3</td>
<td>22±2°</td>
<td>21±3°</td>
</tr>
<tr>
<td>GPT (U/L)</td>
<td>22±3</td>
<td>21.9±2</td>
<td>22±2</td>
<td>22±3</td>
<td>22±3</td>
<td>20±4°</td>
<td>20±4°</td>
</tr>
<tr>
<td>gGT (mg/dL)</td>
<td>32±2</td>
<td>34.6±2</td>
<td>37±2</td>
<td>33±2</td>
<td>33±2</td>
<td>24±3°</td>
<td>23±4°</td>
</tr>
<tr>
<td>CPK (U/mL)</td>
<td>104±19</td>
<td>101.3±21</td>
<td>118±19</td>
<td>95±15</td>
<td>120±25</td>
<td>106.8±24.4</td>
<td>96.1±18.6</td>
</tr>
</tbody>
</table>

*p<0.05 vs. baseline; °p<0.05 vs. Placebo; #p<0.05 vs. Placebo and Verum Low-dose

SBP= Systolic Blood Pressure, DBP= Diastolic Blood Pressure, TC= Total Cholesterol, LDL-C= Low-Density Lipoprotein Cholesterol, HDL-C= High Density Lipoprotein Cholesterol, TG= Triglycerides, Apo= Apolipoprotein, FPG= Fasting Plasma Glucose, GOT= Glutamic-Oxaloacetic Transaminase, GPT= Glutamate Pyruvate Transaminase, gGT= Gamma-Glutamyl-Transferase, CPK= Creatine Phosphokinas
References

9 Nauman MC, Johnson JJ. Clinical application of bergamot (Citrus bergamia) for reducing high cholesterol and cardiovascular disease markers. Integr Food Nutr Metab. 2019;2:10.15761/IFNM.1000249. doi:10.15761/IFNM.1000249


Figure 1

- **Bergamot polyphenols**
  - **HMGCoxA reductase inhibition** → ↓ TC, ↓ LDL-C
  - **NCP1L1 protein transcription inhibition**

- **Opuntia fibers and polyphenols**
  - **AMP Kinase inhibition** → ↓ TG, ↓ FPG
  - **Sequestrin effect**