



Communication

Short-Term Effect of Nutraceutical Fruit Juices on Lipid Metabolism in Patients with Acquired Hypercholesterolemia

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Abstract: The crucial role of dyslipidaemia, especially hypercholesterolemia, in the development of atherosclerosis-related cardiovascular diseases has been extensively documented in genetic, pathologic, observational and intervention studies. The European guidelines for dyslipidaemia management include the possible use of lipid-lowering nutraceuticals to support a relatively large number of natural compounds. In this context, we have conducted a study to investigate whether dietary supplementation with a functional nutraceutical beverage, containing a standardized polyphenolic fraction from fruit, red yeast rice, phytosterols, and berberine complexed with β -cyclodextrin, could positively affect serum lipid concentration in 14 subjects with hypercholesterolemia. After 12 weeks of treatment, dietary supplementation with this nutraceutical combination was associated with significant improvements in total cholesterol, low-density lipoprotein cholesterol, non-high-density lipoprotein cholesterol (non-HDL-C) and apolipoprotein B, compared to baseline. Compliance was excellent and no adverse effects were reported. In conclusion, this study demonstrates that 100 mL of a functional beverage containing lipid-lowering nutraceuticals safely leads to significant improvements in serum lipids in subjects with moderate hypercholesterolemia. Future research is needed to unravel the role that the polyphenols contained in fruit extracts play in the reduction of cholesterolemia and in cardiovascular disease prevention.

Keywords: fruit juices; polyphenols; phytosterols; red yeast rice; berberine-cyclodextrin complex; hypercholesterolemia



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1. Introduction

The important role of dyslipidaemia, especially hypercholesterolemia, in the development of atherosclerosis-related cardiovascular diseases has been fully documented in genetic, pathologic, observational and intervention studies [1–3]. International guidelines recommend improving lipid profiles through lifestyle changes and the use of appropriate drugs, that share the goal of reducing low-density lipoprotein cholesterol (LDL-C) to the lowest possible level in order to prevent the development and progression of atherosclerosis [4,5]. Although statins are the most frequently used drugs for improving lipid profiles and lowering LDL-C levels, their use is limited by their side effects and interactions with other drugs [6,7]. While complete statin intolerance is estimated to occur in less than 5% of the population, the number of people that are intolerant to conventional treatment ranges from 45,000 to 290,000 individuals/year worldwide, with statin intolerance being one of the main reasons for statin discontinuation, poor adherence, and the resulting failure of lipid-lowering treatment [8,9]. In addition, the guidelines indicate that the benefit-risk ratio of these drugs is favorable in the secondary prevention of cardiovascular diseases and for primary prevention in subjects at high or very high overall cardiovascular risk. However,

the ratio is unfavorable in the majority of subjects who have only moderately high LDL-C levels and are not at high cardiovascular risk. There is therefore an unmet therapeutic need in two classes of subjects: patients who are unable or unwilling to take cholesterol-lowering medication despite their high cardiovascular risk; and, health-conscious subjects at low cardiovascular risk who would like to reduce their LDL-C levels, but are not eligible for pharmacological therapy [10]. In this context, the European guidelines for dyslipidemia management consider the possibility of using lipid-lowering nutraceuticals in support of the possible use of a relatively large number of natural compounds [11]. As highlighted in a report by the CTT Collaboration on more than 170,000 subjects, each further reduction of LDL-C by 1 mmol/L (~40 mg/dL), in cholesterol-lowering drug therapy, decreased the risk of revascularization, coronary artery disease and ischemic stroke by about one-fifth. It was underlined that a LDL-C reduction of 3.2 mmol/L (125 mg/dL) could lead to a decrease in risk of about 40–50%, in the absence of increased risk of cancer and non-cardiovascular-related death [12]. One mmol/L is a reduction that is achievable through lifestyle improvements associated with lipid-lowering nutraceuticals [13]. Moreover, it has been estimated that every 1% reduction in LDL-C level corresponds to a reduction in the relative risk of cardiovascular events of greater than 1% [14,15].

It has been known, since the middle of the 20th century, that fruit juices can have a favorable effect on blood lipid profiles and that they are specifically capable of reducing LDL-C thanks to the remarkable anti-oxidant effects of polyphenols and phytosterols [16]. Moreover, the ever-increasing production of food requires a huge number of resources and raw materials are not yet being exploited to maximum efficiency. This leads to the generation of waste, in addition to the waste generated by the leftovers of consumption. Reducing food waste and making suitable use of resources can help to meet the issue of the higher food production, estimated to be 60% higher, that will be needed by the world's population in 2050 [17]. Global food waste also contributes significantly to environmental issues, because of its extensive use of energy and resources as well as the associated greenhouse gas emissions.

The food chains of the most developed countries are characterized by conspicuous food losses (39% during food production and a significant 42% by the consumers) [18]. A large number of the by-products of the various phases of food production have been studied to find ways to limit the environmental and economic impact of food production, and researchers have experimented with new processes for the recovery of valuable components. This may be interesting, in this work's context, as lipid-lowering metabolites can be extracted from fruit waste, using the so-called "zero-waste approach". The industrial juices production from kiwi, grape, Annurca apple and bergamot, generates in all cases around 40–50% of humid residues still rich in valuable secondary metabolites to be extracted and used in food supplements.

A number of studies have underlined the cardiovascular disease prevention activity of various polyphenol- and phytosterols-containing fruit extracts (including kiwi, Annurca apple, bergamot, and grape) that positively affect lipid profiles and have anti-inflammatory, anti-oxidant and hypoglycemic effects [19–23].

The main aim of this study was to evaluate the effects of a blended drink containing kiwi, Annurca apple, bergamot and grape juice (obtained from fruit by-products), phytosterols, red yeast rice and berberine on the lipid profiles of patients with acquired hypercholesterolemia.

2. Results and Discussion

The study involved 14 hypercholesterolemic subjects (five males and nine females with a mean age of 65.5 ± 9.4 years), who underwent clinical, anthropometric and biochemical evaluations at baseline and after four and 12 weeks.

In comparison with baseline, four weeks of nutraceutical juice administration led to a significant reduction in total cholesterol (16%, from 276.9 ± 60.8 to 233.6 ± 50.6 mg/dL; $p < 0.001$), LDL-C (18%, from 181.5 ± 44.4 to 149.7 ± 42.2 mg/dL; $p < 0.001$) (Figure 1),

triglycerides (27%, from 167.9 ± 102.5 to 122.4 ± 59 mg/dL; $p = 0.011$), non-HDL-cholesterol (21% from 216.2 ± 57.7 to 171.4 ± 48.9, $p < 0.001$), and apolipoprotein B levels (12%, from 131.0 ± 33.6 to 113.9 ± 27.3; $p < 0.001$), and there were no differences in HDL-cholesterol, apolipoprotein A1 and HbA1c levels (Table 1).

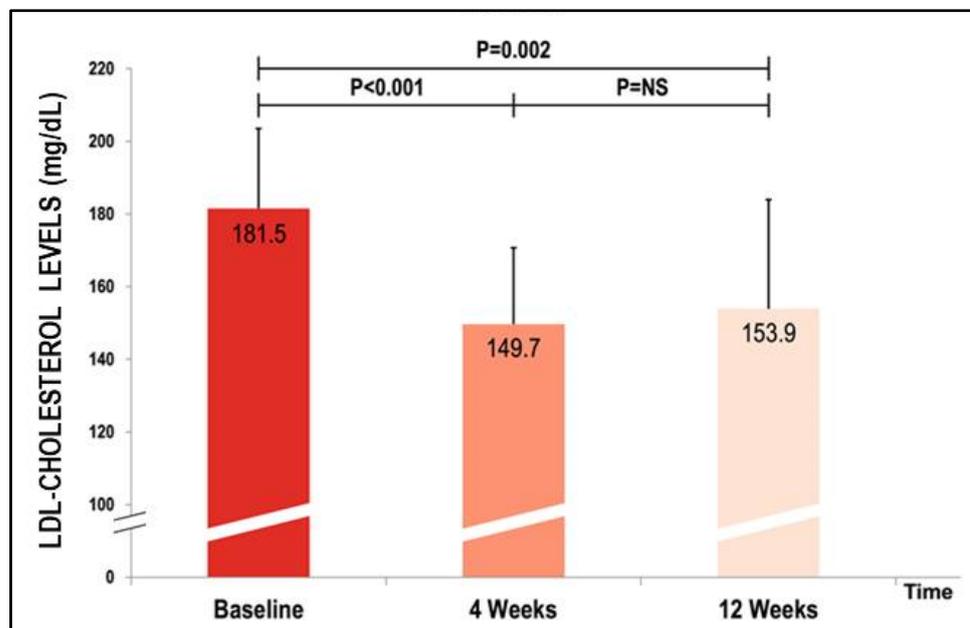


Figure 1. LDL-cholesterol levels at baseline and after four and 12 weeks of follow-up.

Table 1. Biochemical evaluations at baseline and after four and 12 weeks of follow-up.

	Baseline	4 Weeks	12 Weeks	<i>p</i> Baseline vs. 4 Weeks	<i>p</i> Baseline vs. 12 Weeks	<i>p</i> 4 Weeks vs. 12 Weeks
Total cholesterol (mg/dL)	276.9 ± 60.8	233.6 ± 50.6	246.1 ± 63.1	<0.001	<0.001	NS *
LDL-cholesterol (mg/dL)	181.5 ± 44.4	149.7 ± 42.2	153.9 ± 60.5	<0.001	0.002	NS
HDL-cholesterol (mg/dL)	60.7 ± 15.7	62.1 ± 16.6	60.7 ± 16.0	NS	NS	NS
Triglycerides (mg/dL)	167.9 ± 102.5	122.4 ± 59	168.6 ± 163.1	0.011	NS	NS
Non-HDL-cholesterol (mg/dL)	216.2 ± 57.7	171.4 ± 48.9	185.4 ± 65.7	<0.001	<0.001	NS
Apolipoprotein A1 (mg/dL)	155.8 ± 24.0	163.4 ± 27.6	163.8 ± 31.4	NS	NS	NS
Apolipoprotein B (mg/dL)	131.0 ± 33.6	113.9 ± 27.3	118.8 ± 33.0	<0.001	0.009	NS
HbA1c (%)	5.6 ± 0.4	5.6 ± 0.5	5.7 ± 0.4	NS	NS	NS

* NS = Non significant.

In comparison with baseline, 12 weeks of nutraceutical juice administration led to significant reductions in total cholesterol (15%, from 276.9 ± 60.8 to 245.1 ± 63.1 mg/dL; $p < 0.001$), LDL-cholesterol (18%, from 181.5 ± 44.4 to 153.9 ± 60.5; $p = 0.002$) (Figure 1), non-HDL-cholesterol (14% from 216.2 ± 57.7 to 185.4 ± 65.7, $p < 0.001$) and apolipoprotein

B levels (12%, from 131.0 ± 33.6 vs. 118.8 ± 32.9 ; $p = 0.009$), and there were no differences in HDL-cholesterol, apolipoprotein A1, triglyceride and HbA1c levels (Table 2).

Table 2. Clinical and anthropometric characteristics of the study population at baseline, and after four and 12 weeks.

	Baseline	4 Weeks	12 Weeks
Age (years)	65.5 ± 9.4	-	-
Males/females (n)	5/9	-	-
Family history of cardiovascular diseases (n)	12	-	-
History of hypertension (n)	6	-	-
Obesity (n)	1	-	-
Smokers (n)	0	-	-
Heart rate (beats per minute)	62.7 ± 9.4	63.1 ± 8.9	62.6 ± 9.1
Systolic blood pressure (mmHg)	128.9 ± 17.7	125.9 ± 19.7	127.9 ± 18.7
Diastolic blood pressure (mmHg)	80.3 ± 11.1	$79.7.1 \pm 9.9$	80.6 ± 12.1
Height (cm)	171.3 ± 22.7	172.3 ± 21.4	171.8 ± 21.7
Weight (Kg)	73.3 ± 8.7	74.2 ± 10.1	73.0 ± 8.9
BMI (kg/m^2)	24.7 ± 1.7	24.6 ± 1.9	24.7 ± 1.8
Waist circumference (cm)	88.3 ± 7.9	89.1 ± 7.7	88.9 ± 8.1

No significant differences in any of the study parameters were observed between the fourth and twelfth week of follow-up. No adverse events were recorded and none of the patients were forced to discontinue nutraceutical juice administration. Overall compliance over the study period was 96%.

Table 2 shows that there were no significant changes in the subjects' demographic or anthropometric characteristics during the study.

Atherosclerotic cardiovascular diseases are chronic degenerative pathological conditions that can be prevented by changing modifiable risk factors, which is normally done by administering drugs and/or effecting lifestyle changes. However, although major advances have been made in the development and use of risk-factor-modifying drug treatments, the role of lifestyle intervention has been relatively less explored and is generally underutilized [24]. An exception to this can be found in the recent and growing interest in research on, and use of, nutraceuticals and functional foods as agents for the prevention and treatment of atherosclerosis. Nutraceuticals and functional foods can play an important role in primary prevention and may further increase the efficacy of both primary and secondary prevention. Multiple cholesterol-lowering nutraceutical products of different types have been developed [25]. In this study, a novel nutraceutical beverage was used to lower LDL-cholesterol by an average of 18% within one month and has been shown to have several advantages over other nutraceutical products. The use of entirely natural ingredients makes it more attractive to people who wish to avoid artificial substances and, unlike the many nutraceuticals packaged as pills or vials, its presentation as a fruit juice allows it to be considered a food rather than a quasi-pharmacological product. Pharmaceutical-like packaging can act as a barrier, especially in subjects that are reluctant to take medication as a matter of principle. Finally, its value in terms of vitamin and fiber intake can positively contribute to a more balanced diet.

There are two main categories of subject who may benefit from the nutraceutical beverage used in this study. The first includes those who refuse to take medicinal products. Previous studies have shown that up to 50% of subjects that are prescribed a statin stop taking it within a year [26]. Although non-compliance is a multifactorial phenomenon, it is known that some of these subjects stop taking their medication because they have a

personal dislike of taking a pill daily, and these people may well find the nutraceutical drink described in this study an acceptable alternative, not least because its packaging and presentation does not resemble that of a pharmacological product.

The second category includes subjects who wish to lower their LDL-cholesterol levels further than the level obtained by the administration of their on-going drug treatment, and health-conscious subjects who wish to reduce their LDL-C levels despite their low cardiovascular risk, for purposes of primary prevention. Neither of these groups would meet the guideline-based criteria for starting a new or additional drug treatment, but might both benefit from additional LDL-cholesterol lowering, for which there are no currently known protocols. For these subjects, the nutraceutical beverage developed in this study may be an interesting option.

We herein provide preliminary data on a nutraceutical product that is composed entirely of natural ingredients and presented as a fruit juice, and show how it significantly improved cholesterol profiles (including LDL-C levels) after only four weeks. The product's non-pharmacological appearance, natural origin, and nutritional value could help increase compliance among individuals seeking to avoid pharmacological agents and could be a viable option for individuals who do not have an indication for drug treatment, but want to improve their cardiovascular risk profile.

Despite its relevant findings and practical implications, this study is not without limitations. We acknowledge that the small sample size and open-label format mean that the study should be confirmed by new randomized double-blind trials. In addition, the relatively short follow-up period means that an assessment of the possible occurrence of adaptation phenomena is impossible. However, these phenomena have not been documented to date. Further research is needed to uncover the reasons behind, and mechanisms for, the effects observed in the study. For instance, the effect on serum lipids is likely mediated in part by a change in the gut microbiota induced by fruit polyphenol supplementation. Available experimental data suggest that supplementation with bergamot and polyphenolic fractions is able to exert a beneficial effect on the composition of the gut microbiota [27]. However, no specific evidence for simultaneous supplementation with these nutraceutical compounds is available to date [28].

3. Materials and Methods

3.1. Subjects

Fourteen subjects were enrolled in the study: five males and nine females with a mean age of 65.5 ± 9.4 years. The subjects underwent clinical, anthropometric and biochemical evaluations at baseline and after four and 12 weeks (Table 1). The study population consisted of hypercholesterolemic subjects aged >18 years who required primary prevention treatment because of hypercholesterolemia, but who refused to take, or could not tolerate, statins. Subjects were excluded from the study if they showed any clinical signs of chronic infection, hepatic, renal or gastrointestinal disease, or any acute disease requiring treatment. The exclusion criteria also included diabetes, a history of significant metabolic disease and the use of lipid-lowering or anti-coagulation drugs over the previous six months. All subjects provided their informed consent before entering the study.

3.2. Study Protocol

The study protocol involved the daily administration of a nutraceutical juice for 12 weeks. All the enrolled subjects were given 100 mL bottles of the juice and were instructed to shake and drink one bottle every morning between breakfast and lunch. All the unused bottles were retrieved for inventory purposes, and compliance was assessed by counting the number of empty bottles returned at specified clinic visits. These four fruits were selected because of their intrinsic properties and ability to ameliorate lipidic profiles in blood serum, as supported by recent papers and a meta-analysis.

3.3. The Juice

Each 100 mL bottle contained:

- (1) Kiwi [29], Annurca apple [22], bergamot [30] and grape juice [31];
- (2) Two grams of phytosterols;
- (3) Red yeast rice containing 2.9 mg of monacolins from *Monascus purpureus*;
- (4) 100 mg of berberine complexed with β -cyclodextrin.

The four types of fruit were selected on the basis of the findings of recent studies or meta-analysis indicating their intrinsic capacity to improve blood serum lipid profiles. The phytosterol dose was chosen on the basis of the average efficacious dose identified in a meta-analysis of randomized clinical trials [23]. The red yeast rice extract was certified to contain purified monacolins, without any chromatographically detectable levels of dehydromonacolins, decalin derivatives, or contaminants. Although berberine was complexed with β -cyclodextrin, it retained its bitter taste, thus limiting its dose. At the beginning of our investigation, we used a water solution of monacolin, berberine and phytosterols. Unfortunately, the unpleasant taste had a significant negative impact on compliance and the volunteers soon left the trial.

Juice Processing and Storage

The raw materials and semi-finished products were purchased from qualified suppliers, and each product was accompanied by a specific technical data sheet indicating the origin of the raw material, the microbiological, physicochemical and organoleptic characteristics of the product, the type of packaging, the storage methods, the presence or absence of GMOs and/or allergens, and the expiry date.

The raw materials in the nutraceutical juice do not require any particular storage conditions. They are aseptic and non-perishable (except for mint, which is frozen and stored at $-18\text{ }^{\circ}\text{C}$) and were stored on shelves in the designated cool and dry area of the organic raw materials warehouse.

The raw materials used to prepare the nutraceutical juice were weighed and placed in a Roboqbo (RCQ) vacuum cooking system. In the first cooking phase, the oily active ingredients were mixed with soy lecithin and a part of the water and kiwi fruit (i.e., about 10% of the finished product). Once the mixture reached a temperature of $70\text{ }^{\circ}\text{C}$, it was passed through a GEA homogenizer, which is ideal for the high-pressure treatment of nanodispersions and cell lysis and guarantees high performance at a pressure of 500 bar.

At this point, the active ingredient mixture was mixed with the other raw materials before being heated to a temperature of $85\text{ }^{\circ}\text{C}$ and then conveyed to the filling area, where it was used to fill the 100 mL bottles.

Before the product was unloaded, the RCQ manager took a sample in the laboratory and checked that the physicochemical properties met the required specifications. The nutraceutical juice was pasteurized at $85\text{ }^{\circ}\text{C}$ for 10' and then cooled until the temperature at the middle of the bottle was $<40\text{ }^{\circ}\text{C}$.

3.4. Assessments

Clinical evaluations included a determination of height, body weight, waist circumference and arterial blood pressure, and an electrocardiographic examination. Blood samples taken after a 12-h fast were used to measure total cholesterol, LDL-cholesterol, high-density lipoprotein cholesterol (HDL-C), apolipoprotein A1, apolipoprotein B, triglyceride and HbA1c levels using standard clinical procedures.

Upon enrollment, the subjects were asked to maintain their dietary habits and to not change their physical-activity routines over the course of the study.

3.5. Statistical Analyses

Statistical analyses were carried out using R Studio, Version 4.2.1. The baseline characteristics of the study population as a whole are expressed in absolute numbers (percentages) in the case of binary and categorical variables, as mean values (standard deviation) in the

case of normally distributed continuous variables, and as median values (interquartile range) in the case of non-normally distributed continuous variables. Distribution normality was ascertained via a visual inspection of the histograms. Mean baseline blood-test values were compared separately with those obtained after four and 12 weeks using two-tailed paired t-tests, whereas trends across the three time points were analyzed using three-way analysis of variance (ANOVA). Statistical significance was considered at a nominal alpha value of 0.05, and all tests were two-sided.

4. Conclusions

In conclusion, the study shows that 100 mL of dietary supplementation with standardized kiwi, Annurca apple, bergamot and grape juice extracts with phytosterols, red yeast rice and berberine complexed with β -cyclodextrin, safely provides significant improvements in serum lipids in subjects with moderate hypercholesterolemia. Although the potential disease prevention and therapeutic effects of polyphenols have been documented in the literature [32], this is the first study with this peculiar combination. In spite of the small sample size of the pilot study and the relatively short duration of the treatment, the preliminary results could prompt further investigations. Our findings are not definitive and should be confirmed with the rigor of long-term randomized clinical trials to be conclusive.

In addition, future research is needed to understand the role played by the polyphenols that are contained in the fruit-by-product extracts in the reduction of cholesterolemia and in cardiovascular disease prevention.

5. Patents

Italian patent Ardissino D. 19/05/2022 n. 102020000005818.

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Institutional Review Board Statement: Ethical review and approval were waived for this study due to the observational nature of the protocol.

Informed Consent Statement: Patient consent was waived as this is a non-therapeutic protocol based on food supplements.

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Conflicts of Interest: The authors declare no conflict of interest.

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