Nutrafoods (2022) 2:457-463 DOI 10.17470/NF-022-0054

Original research

Effect of Cardio 360° - Prevent® on total, HDL- and LDL-cholesterol levels: a pre- and post-observational study

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Abstract

Cardiovascular diseases (CVDs) are the leading cause of death globally. Hypercholesterolaemia, particularly low density lipoprotein (LDL) cholesterol, is directly involved in the atherosclerosis process. Consequentially, lowering cholesterolaemia and LDL-cholesterol serum levels will reduce cardiovascular risk. This observational study analyzed the results of 120 daily treatments with the food supplement (Cardio 360° - Prevent®) based on extracts of *Ipomoea batatas*, *Crataegeus Laevigata*, *Berberis aristata*, *Olea europaea*, *Camellia sinensis* and *Polygonum cuspidatum* in 25 individuals affected by mild hypercholesterolaemia.
At the end of treatment, improvements were observed in total cholesterol (TC), LDL-cholesterol (LDL-C), HDL-cholesterol (HDL) and triglycerides (Trig.) serum levels when compared with baseline values. In particular, the supplementation of Cardio 360° - Prevent® was associated with a significant reduction in TC (-14.8 %), LDL (-19.3%) and triglycerides (-20.8%). A slight increase in HDL serum levels (+1.2%) was observed. Cardio 360° - Prevent® could be considered a new strategy and as an effective tool for the treatment of non-severe Dyslipidaemia, particularly mild hypercholesterolaemia. Further large-scale clinical trials are needed to evaluate efficacy, safety and tolerability to the mixtures of extracts used in clinical management of dyslipidaemias.

Keywords: Hypercholesterolaemia, cardiovascular disease, Berberine, monacolin K, Poliferina®, Cardio 360° - Prevent®

Introduction

Cardiovascular diseases (CVDs) are the leading cause of death globally. Atherosclerotic CVD (ASCVD) is the major cause of premature death in Europe and the main determining factor of disability, as reported by World Health Organization (WHO). [1] As well demonstrated by current evidence, the management of serum cholesterol and triglyceride levels can reduce cardiovascular risk, and consequently the probability of CVDs or their progression. [2] Dyslipidaemia is a major known risk factor for CVDs. [3] It is identified by significant alterations of blood lipid levels, with particular reference to increased levels of total cholesterol (TC), low density lipoproteins (LDL) and triglycerides (Trig.).

With regards to the association between lipid serum levels and cardiovascular risk evaluation, evidence suggests that hypercholesterolaemia has a direct causal relationship with arteriosclerosis and related clinical events. [4] In fact, LDL-cholesterol (LDL-C) is directly involved in the atherosclerosis process, in which foam cells – derived from macrophages – play a key role in determining the triggering of pathological mechanisms that lead to endothelial lesions of the vessel, culminating in the formation of atherosclerotic plaque. [5]

Using an etiological distinction, it is possible to consider two types of hypercholesterolaemia: primary and secondary. Primary hypercholesterolaemia is caused by genetic mutations that result in defective elimination of LDL-cholesterol and triglycerides, or reduced production or excessive elimination of HDL-cholesterol. Secondary hypercholesterolaemia is very common in industrialized countries and is associated with several secondary causes, including lifestyle factors (poor eating habits and lack of physical inactivity), metabolic syndrome, type 2 diabetes, alcohol abuse, chronic kidney disease, hypothyroidism, primary biliary cirrhosis or other cholestasis related hepatic pathologies etc. [6]

Regardless of the type of dyslipidaemia, modifications in plasma LDL-cholesterol levels are casually associated to the degree of risk for cardiovascular disease, as demonstrated in several epidemiologic studies, [7] controlled intervention studies [8] and Mendelian randomization studies. [9]

Although a safety threshold has not been set, below which is no longer possible to identify a causal association between LDL-cholesterol blood levels and cardiovascular risk, it can be argued that there is a correlation between lower LDL-cholesterol levels and a lower risk for cardiovascular diseases. [10]

Considering the causal relationship between LDL hypercholesterolaemia and arteriosclerosis, any treatment of dyslipidaemia should aim to reduce serum LDL-C levels. As supported by the guidelines for the clinical management of dyslipidaemias produced by the European Society of Atherosclerosis (ESA) and the European Society of Cardiology (ESC), each reduction of plasma LDL-C levels – if sufficiently extended over time – will lead to a reduction in cardiovascular risk, regardless of baseline value. [7]

We can identify three areas of treatment for dyslipidaemias: modification of diet and lifestyle; use of nutraceuticals and functional foods; pharmacological treatment.

Poli *et al.* provided useful indications on a therapeutic approach to hypercholesterolaemia; in particular they proposed a 'reasoned approach' to lower cholesterolaemia, based on simultaneous integration of lifestyle interventions (diet and physical activity), use of supplements and functional foods and pharmacological drugs in cardiovascular prevention. [11]

The classic step-by-step therapeutic management of dyslipidaemias (a lifestyle intervention programme, which if unsuccessful is followed using nutraceuticals and/or pharmacological drugs) has not been shown to be effective. In fact, dietary interventions or positive

lifestyle modifications do not significantly reduce total and LDL-cholesterolaemia. [12] Recent evidence shows that a healthy diet and active lifestyle can reduce cardiovascular risk through different mechanisms that are independent of a reduction in LDL-C. [13]

Until approximately 15–20 years ago, clinical management of hypercholesterolaemia focused only on dietary interventions and prescribed drugs, especially statins. The main drugs available and used in this clinical context were statins, fibrates, nicotinic acid and bile-sequestrating drugs.

Due to the increased incidence of dyslipidaemia and cardiovascular diseases, there has been an upsurge in the use of nutraceuticals in recent years. Based on current knowledge, nutraceuticals could exert a significant lipid-lowering activity, through multiple mechanisms. Nutraceuticals used for the treatment of hypercholesterolaemia – acting simultaneously at multiple levels of the vascular damage induced by the conditions produced by hyperlipidaemia – are valid lipid-lowering agents, especially when used in combination with specific dietary patterns or lifestyle interventions, drugs or other nutraceuticals. [14] Furthermore, a significant number of results derived from clinical trials provide epidemiological data to support a valid safety and tolerability profile of many nutraceuticals with proven lipid-lowering action, even in patients who do not tolerate statins. [15]

There are many nutraceuticals with proven efficacy used for clinical management of dyslipidaemia. In this clinical context the main molecules used are plant sterols and stanols, red yest rice, dietary fibre, beta-glucan, Berberine, bergamot extract, soy derivates and many other cholesterol-lowering elements. These active ingredients just mentioned, found in nutraceuticals which are usually used for the treatment of dyslipidaemia, have shown a significant cholesterol-lowering activity (5-25%) when used in monotherapy. But if they were combined, they could possibly interact, decreeing a superior cholesterol-lowering effect. [16]

Poli *et al* [11] provide practical indications on the use of cholesterol-lowering nutraceuticals and on identification of individuals who could benefit from treatment. As with any supplement, the choice of potential candidates must follow a clinical evaluation of lowing-cholesterol needs, risk/benefit ratio assessment, metabolic profile and patient-specific pathophysiological characteristic.

In this work we evaluated the efficacy of the food supplement Cardio – 360° Prevent® in the treatment of hypercholesterolemia. Its active ingredients are *Ipomoea batatas* extract, *Crataegus laevigata* dry extract, Berberine (from *Berberis aristata*), *Olea europaea*, *Camellia sinensis* and *Polygonum cuspidatum* extracts. The main compounds of this supplement are briefly described below.

- Berberine
  Berberine is an alkaloid extracted from the root of *Berberis aristata* DC. It has a significant effect in reducing TC and LDL-C in individuals of any age with dyslipidaemia and triglycerides in individuals with diabetes with altered lipid profiles. [17] It mainly acts by upregulating LDL-receptor (LDL-R) and downregulating proprotein convertase subtilisin/kexin type 9 (PCSK-9). [18] It follows that the association between Berberine and statins or monacolins is successful because Berberine cancels the negative effect that statins have on PCSK9, ultimately enhancing their action. [19] Berberine seems to be able to reduce LDL-cholesterol by approximately 10-20%. [20]

- Red yeast rice
  Monacolin K and Ka are the molecules derived from fermentation of rice (*Oryza sativa* L.) by fungi (*Monascus purpureus Went*). As monacolin shows the same chemical structure of Lovastatin – a common statin used for treatment of hypercholesterolaemia – it also acts to inhibit enzyme HMG-CoA-re-

ductase, reducing the endogenous synthesis of cholesterol. At a dose of between 3mg and 10mg/day, monacolin K can result in a reduction of LDL-cholesterol by 20–25%. [21]

- *Ipomoea batatas*
  L. Batata extract shows positive effects in treating hyperglycaemia and hyperlipidaemia, increasing the function of pancreatic cells and reducing serum lipid levels. [22]
  In addition, *L. Batata* extract seems to be an antioxidant, reducing reactive oxygen species (ROS) production and protecting cells from ageing. [23]

- *Crataegus Laevigata*
  Hawthorn extract is an edible plant of the rosacea family and is used in traditional medicine as a remedy to improve cardiovascular health. It contains various active compound such as flavonoids and triterpenes, which have antihypertensive and cardiotonic properties, reducing cardiovascular risk factors such as hypertension, thrombosis, etc. [24]

- *Camellia sinensis* L.
  Green tea flavonoids – in particular flavan-3-ols (catechins) – have been inversely associated with a reduction of cardiovascular risk factors. [25] Some clinical studies have observed that the use of dry extract of the tea *Camellia sinensis* is associated with a significant reduction in LDL-cholesterol levels in study participants, especially in men and women with a BMI of 30 or greater. [26, 27]

- *Polygonum cuspidatum* (sieb. et zucc.)
  Water extract of *Polygonum cuspidatum* is rich in resveratrol. It is a polyphenolic compound which seems to modulate positively lipid metabolism, lowering LDL-cholesterol and serum lipid levels, inhibiting synthesis of triglycerides in the liver and reducing lipid hepatic accumulation. However, the scientific literature is discordant on the on the improvement of the serum lipid levels exerted by resveratrol, therefore further studies are needed. [28]

Materials and methods

Study overview

This observational study analyzed the results of 120 days of daily treatment with the food supplement Cardio 360° - Prevent® in 25 individuals aged between 42 and 86. No control or placebo groups were involved in this preliminary work.

The supplement was proposed by some GPs to individuals who showed mild hypercholesterolaemia without the presence of other pathologies. The participants took one tablet per day of Cardio 360° - Prevent® for 120 days; each tablet contains 150mg of Ipomoea batatas extract, 6mg of flavonoids (from *Crataegus laevigata* dry extract), 125mg of *Berberis aristata* extract, 2.8mg of monacolin k (from red yeast rice – 56mg) 200µg of folic acid and Poliferina®. Poliferina® corresponds to a highly standardized mixture of *Olea europaea* (of which 0.14mg oleuropein), *Camellia sinensis* (of which 0.7 mg polyphenols), *Polygonum cuspidatum* extracts (of which 0.6mg resveratrol) and Q10 Coenzyme (0.05mg). Cardio 360° - Prevent® was used under the rationale of supporting circulatory function through the synergistic action of its components.

Participants

All 25 recruited participants were affected by polygenic hypercholesterolemia and were asked to implement lifestyle interventions (regular physical exercise and diet) that could have a hypolipidemic effect. The following exclusion criteria were considered: recognized intolerance to NUT components, diagnosis of severe pathologies, high or very high CV risk, severe liver disease, non-pharmacologically controlled thyroid disease, active peptic ulcer, chronic inflammatory bowel disease, pregnancy and breastfeeding, and treatment with lipid-lower-

ing therapy in the 30 days before enrolment.

The average age of participants was 59 ± 10, with a BMI of 25.7 ± 4.3. The numbers of men and women were 10 (41.6%) and 14 (58.3%) respectively. Anthropometric values, such as weight, height, BMI, TC, LDL, HDL and trig. were measured for all participants at the baseline and at the end of treatment. Data studies and analysis were conducted in accordance with good clinical practice rules fixed by the Declaration of Helsinki and in accordance with the European Union Directive 2001/20/EC. [29] Each patient signed a consent form and privacy policy documents and approved data analysis and publishing.

Statistical analysis

Descriptive statistics of quantitative variables are reported as mean and standard deviation. A paired t-test was used to verify the effectiveness of the supplement on the levels of TC, LDL, HDL and trig. Furthermore, the percentage change and effect size (Cohen's D) was reported. The results are shown graphically (**Fig. 1**), with the real values and the corresponding box plot. All processing was performed with Excel or SPSS 22.0. The significance level is set at 0.05.

Results

The trial began with 25 participants. One participant abandoned the supplement during the trial period due to unrelated health problems; the other participants finished the course, taking the supplement on at least 90% of the specified days. At the time of inclusion (T0), participants enrolled at the baseline had the following average values: TC (248.5 ± 18.6 mg/dL), HDL (58.2 ± 12.4 mg/dL), Trig (134.9 ± 71.4 mg/dL), LDL (163.1 ± 16.1 mg/dL). At the end of the supplement period, TC=211.8 ± 28.9 (t=6.33; p<0.001) with a percentage variation of -14.7%, with an effect size =1.29 (very large effect); HDL = 58.9 ± 14.2 (t=0.50; p=0.62) with a percentage variation = 1.2%, with an effect size = 0.02 (very small effect); Trig = 106.9 ± 37.8 (t=2.36; p=0.03) with a percentage variation = -20.8%, with an effect size = 0.48 (medium effect); finally, LDL = 131.6 ± 24.4 (t=5.94; p<0.001) with a percentage variation= -19.3%, with an effect size =1.21 (large effect). To summarize, the supplement significantly decreased the level of TC, LDL and Trig. It is interesting to note that cholesterol levels significantly decreased close to physiological levels. These results are shown in **Fig 1**.

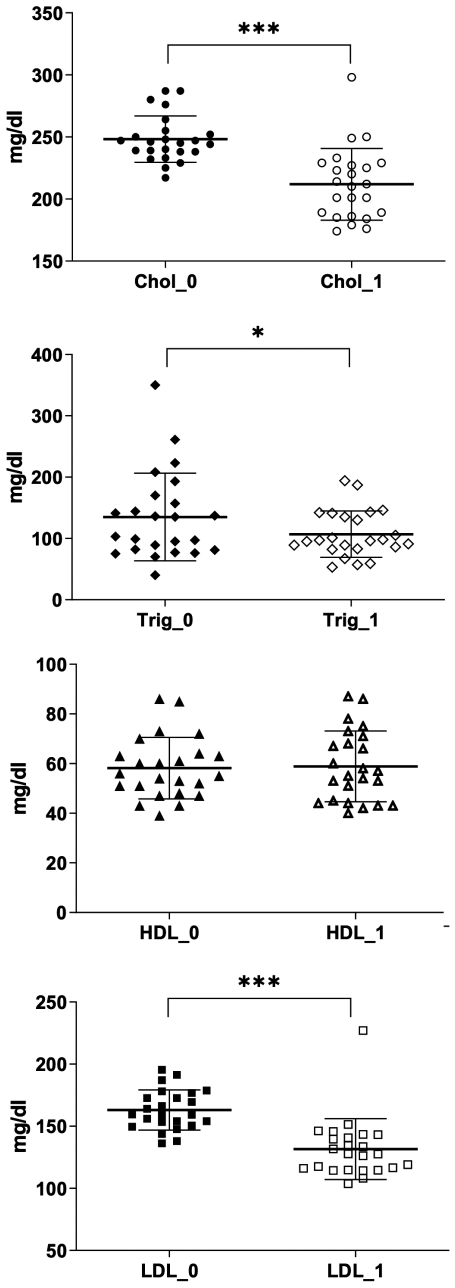

Figure 1: Graphical representation of TC, HDL, Trig and LDL level at T_0 and T_1. *=significant; ***=extremely significant.

Conclusions

Based on the results of the current study, we can consider the use of Cardio 360° - Prevent® as a new therapeutic strategy and effective tool for the treatment of non-severe dyslipidaemia, particularly hypercholesterolaemia. In fact, the results showed that Cardio 360° - Prevent® improved serum lipid levels, significantly reducing TC, LDL- C and triglycerides (Trig).

The nutraceutical supplement Cardio 360° - Prevent® is much more easily accessible than prescribed drugs, being distributed by large-scale retail trade. This aspect could help medium- and long-term compliance among individuals once appropriate counselling on proper usage is given by physicians, medical doctors, nutritionists or pharmacists.

Further large-scale clinical trials are needed to evaluate efficacy, safety and tolerability of mixtures of extracts used in clinical management of dyslipidaemias.

Conflict of Interest

None.

References

1. World Health Organisation (WHO). Cardiovascular diseases (CVDs) (2015). Available from: www.who.int/mediacentre/factsheets/fs317/en/ (accessed 28 August 2016)

2. Getz GS, Reardon, CA (2015) Atherogenic lipids and macrophage subsets. Curr Opin Lipidol 26:357–361

3. Söderström LÅ, Gertow K, Folkersen L *et al* (2014) Human genetic evidence for involvement of CD137 in atherosclerosis. Mol Med. 20:456–465

4. Italian Association of Dietetics (2014) Nutritional and medical therapy of dyslipidemias. Available from: www.adiitalia.org/20111-08-09-02-47-49/kunena-2014-05-2 (Accessed: 06 May 2022)

5. Rizzo M, Kotur-Stevuljevic J, Berneis K, *et al* (2009) Atherogenic dyslipidemia and oxidative stress: a new look. Transl Res. 153(5):217–223

6. Hofbauer S, Wiesli P (2020) CME: Primäre und sekundäre Hypercholesterinämie [CME: Primary and Secondary Hypercholesterolemia]. Praxis 109 (10):755–762

7. Catapano A, Graham I, De Backer G, *et al* (2016) ESC/EAS Guidelines for the Management of Dyslipidaemias: The Task Force for the Management of Dyslipidaemias of the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS) Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). Atherosclerosis 253:281–344

8. Fulcher J, O'Connell R, Voysey, *et al* (2015) Efficacy and safety of LDL-lowering therapy among men and women: meta-analysis of individual data from 174,000 participants in 27 randomised trials. Lancet 385:1397–1405

9. Ference BA (2015) Mendelian randomization studies: using naturally randomized genetic data to fill evidence gaps. Current opinion in lipidology 26(6):566–571

10. Masana L, Girona, J, Ibarretxe, D, *et al* (2018) Clinical and pathophysiological evidence supporting the safety of extremely low LDL levels – The zero-LDL hypothesis. J Clin Lipidol 12(2):292–299

11. Poli A *et al* (2018) Nutraceuticals and functional foods for the control of plasma cholesterol levels. An intersociety position paper. Pharmacol Res. 134:51–60

12. Brunner EJ, Rees K, Ward K, Burke M, Thorogood M (2007) Dietary advice for reducing cardiovascular risk. Cochrane Database Syst Rev (4):CD002128

13. Rees K, Dyakova M, Wilson N, Ward K, Thorogood M, Brunner E (2013) Dietary advice for reducing cardiovascular risk. Cochrane Database Syst Rev (12):CD002128

14. Sahebkar A, Serban Maria-Corina, Gluba-Brzózka A, *et al* (2016) Lipid-modifying effects of nutraceuticals: an evidence-based approach. Nutrition 32(11–12):1179–1192

15. Cicero AF, Fogacci F, Colletti A (2017) Food and plant bioactives for reducing cardiometabolic disease risk: an evidence based approach. Food Funct 8(6):2076–2088

16. Johnston TP, Korolenko TA, Pirro M, Sahebkar A (2017) Preventing cardiovascular heart disease: Promising nutraceutical and non-nutraceutical treatments for cholesterol management. Pharmacological research 120:219–225

17. Bertuccioli A, Moricoli S, Amatori S, *et al* (2020) Berberine and Dyslipidemia: Different Applications and Biopharmaceutical Formulations Without Statin-Like Molecules-A Meta-Analysis. J Med Food 23(2):101–113

18. Kong W, Wei J, Abidi P, *et al* (2004) Berberine is a novel cholesterol-lowering drug working through a unique mechanism distinct from statins. Nat Med 10(12):1344–1351

19. Momtazi AA, Banach M, Pirro M, *et al* (2017) Regulation of PCSK9 by nutraceuticals. Pharmacol Res 120:157–169

20. Dong H, Zhao Y, Zhao, L, Lu F (2013) The effects of berberine on blood lipids: a systemic review and meta-analysis of randomized controlled trials. Planta Med 79(6):437–446

21. Li Y *et al* (2014) A meta-analysis of red yeast rice: an effective and relatively safe alternative approach for dyslipidemia. PLoS One 9(6):e98611

22. Naomi R, Bahari H, Yazid MD, *et al* (2021) Potential Effects of Sweet Potato (*Ipomoea batatas*) in Hyperglycemia and Dyslipidemia – A Systematic Review in Diabetic Retinopathy Context. Int J Mol Sci 22(19):10816

23. Lin K-H, Low P-Y, Chao PY, *et al* (2017) Antioxidant properties and glucose uptake effect of ethanol extracts from different sweet potato leaves prepared by lyophilization and oven- drying at 40°C. Curr. Nutr Food Sci 13:227–236

24. Nabavi SF, Habtemariam S, Ahmed T, *et al* (2015) Polyphenolic composition of crataegus monogyna Jacq: From Chemistry to Medical Applications. Nutrients 7(9):7708-7728

25. Keller A, Wallace TC (2021). Tea intake and cardiovascular disease: an umbrella review. Ann Med 53(1): 929–944

26. Batista Gde A, Cunha CL, Scartezini M, *et al* (2009) Prospective double-blind crossover study of Camellia sinensis (green tea) in dyslipidemias. Arq Bras Cardiol 93(2): 128–134

27. Huang LH, Liu CY, Wang LY, *et al* (2018) Effects of green tea extract on overweight and obese women with high levels of low density-lipoprotein-cholesterol (LDL-C): a randomised, double-blind, and cross-over placebo-controlled clinical trial. BMC Complement Altern Med 18(1): 294

28. Riccioni G, Gammone MA, Tettamanti G, *et al* (2015) Resveratrol and anti-atherogenic effects. Int J Food Sci Nutr 66(6):603–610

29. World Medical Association (2001) World Medical Association Declaration of Helsinki. Ethical principles for medical research involving human subjects. Bulletin of the World Health Organization 79(4): 373–374