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Original Research

Ateronorm Plus® – effects on total, HDL- and LDL-cholesterol levels and its hypothetical action on weight control: a pre- and post-observational study

Abstract

Cardiovascular diseases are the primary cause of death worldwide. Elevated levels of low-density lipoprotein cholesterol (LDL-C), known as hypercholesterolaemia, play a direct role in the development of atherosclerosis, a condition where plaque builds up in the arteries. Reducing hypercholesterolaemia and LDL-C levels can lower the risk of cardiovascular events. This observational study examined the effects of the nutraceutical supplement Ateronorm Plus® (marketed by Aquaviva srl) on 30 individuals with mild hypercholesterolaemia. Ateronorm Plus® contains extracts of berberine, red yeast rice (monacolin K and Ka) and Polygonum cuspidatum. After 120 days of treatment, improvements were noted in serum levels of total cholesterol (TC), LDL-C, high-density lipoprotein cholesterol (HDL-C) and triglycerides (Trig.) compared to baseline values. Specifically, Ateronorm Plus® supplementation was associated with a significant reduction in TC (-21.7%), LDL-C (-26.3%), and Trig. (-16.4%), along with an increase in HDL serum levels (+9.3%). Furthermore, a greater weight loss and improved metabolic parameters were observed in participants undergoing supplementation with Ateronorm Plus® during the study period. Ateronorm Plus® may represent a novel approach and an effective tool for managing mild dyslipidaemia, particularly mild hypercholesterolaemia. However, further large-scale clinical trials are necessary to assess the efficacy, safety and tolerability of the extract mixtures used in the clinical management of dyslipidaemias.

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Introduction

Cardiovascular diseases (CVDs) are the primary cause of death worldwide. Atherosclerotic CVD (ASCVD) is the leading cause of premature death in Europe and a major contributor to disability, according to the WHO [1]. Evidence shows that managing cholesterol and triglyceride levels can decrease cardiovascular risk and potentially prevent or slow the progression of CVDs [2]. Dyslipidaemia characterized by significant changes in blood lipid levels, particularly elevated levels of total cholesterol (TC), low-density lipoproteins (LDL), and triglycerides (Trig.), is a well-known risk factor for CVDs [3].

Regarding the correlation between lipid serum levels and the assessment of cardiovascular risk, research indicates a direct link between hypercholesterolaemia and atherosclerosis, along with its associated clinical consequences [4]. LDL-cholesterol (LDL-C) plays a crucial role in the progression of atherosclerosis, where foam cells, originating from macrophages, are instrumental in initiating pathological processes that result in endothelial lesions of blood vessels, ultimately leading to the formation of atherosclerotic plaques [5].

Hypercholesterolaemia can be categorized into two distinct types: primary and secondary. Primary hypercholesterolaemia stems from genetic mutations that disrupt the proper elimination of LDL-C and Trig. or lead to a decrease in HDL-C production or excessive elimination. Secondary hypercholesterolaemia is prevalent in industrialized countries and is linked to a variety of secondary factors, including lifestyle choices (poor eating habits and physical inactivity), metabolic syndrome, type 2 diabetes, alcohol abuse, chronic kidney disease, hypothyroidism, primary biliary cirrhosis or other liver conditions related to cholestasis [6].

Regardless of the specific type of dyslipidaemia, changes in LDL-C levels in the blood are consistently linked to the degree of CVD risk. This relationship has been confirmed through various types of studies, including epidemiological investigations [7], controlled intervention trials [8] and Mendelian randomization studies [9].

While there is no definitive 'safety threshold' below which the causal association between LDL-C levels and cardiovascular risk disappears, it is reasonable to suggest that lower LDL-C levels are correlated with a reduced risk of CVDs [10].

Treating hypercholesterolaemia not only improves an individual's lipid profile but improves their metabolic profile in general. In this regard, scientific literature defines a clear cause and effect relationship between CVD and insulin resistance (IR), which is typical of individuals with obesity and metabolic disorders. IR is characterized by a reduced tissue response to insulin, a hormone capable of facilitating the entry of glucose into cells to be used as an energy substrate. The excess glucose remains in circulation, causing hyperglycaemia. In response to inadequate energy absorption, the tissues modify their metabolic pathways, supporting disorders such as inflammation, obesity, dyslipidaemia, atherosclerosis, endothelial dysfunction and hypertension.

Given the established link between high LDL-C levels and arteriosclerosis, it is imperative that any treatment of dyslipidaemia focuses on reducing serum LDL-C levels. This approach is endorsed by the clinical management guidelines issued by European Society of Atherosclerosis (ESA) and the European Society of Cardiology (ESC), which emphasize that each reduction in plasma LDL-C levels, when sustained over time, contributes to lowering cardiovascular risk, regardless of initial baseline levels [7].

Treatment for dyslipidaemia can be categorized into three main areas: dietary and lifestyle modifications; use of nutraceuticals and functional foods; pharmacological treatment. Poli *et*

al. (2018) proposed a comprehensive therapeutic strategy for managing hypercholesterolaemia, which advocated for a balanced approach that combines lifestyle changes (dietary adjustments and increased physical activity) with the use of supplements, functional foods and appropriate pharmacological drugs [11].

The traditional 'step-by-step' therapeutic approach to managing dyslipidaemias, which involves a lifestyle intervention program followed by nutraceuticals and/or pharmacological drugs, if necessary, has been proven to be ineffective. In fact, dietary interventions or positive lifestyle changes do not significantly reduce TC or LDL-C levels [12]. Recent evidence suggests that a healthy diet and active lifestyle can lower cardiovascular risk through mechanisms unrelated to LDL-C reduction [13].

Until 15–20 years ago, the clinical treatment of cholesterol primarily revolved around dietary interventions and prescribed drugs, particularly statins. Commonly prescribed medications for this clinical context included statins, fibrates, nicotinic acid and bile-sequestrants.

The rise in dyslipidaemia and CVD has led to increased use of nutraceuticals in recent years. Specifically targeted at treating high cholesterol, nutraceuticals address multiple aspects of vascular damage caused by hyperlipidaemia, making them effective lipid-lowering agents, especially when combined with specific dietary plans or lifestyle interventions, drugs or other nutraceuticals [14]. Moreover, findings from numerous clinical trials provide epidemiological evidence supporting the safety and tolerability of many nutraceuticals with proven lipid-lowering effects, even among individuals who cannot tolerate statins [15].

Numerous nutraceuticals including plant sterols and stanols, red yeast rice, dietary fibre, beta-glucan, berberine, naringin, bergamot extract, soy derivates and various other cholesterol-lowering elements have a proven effectiveness in managing dyslipidaemia. Individually, these active ingredients, commonly found in nutraceutical formulations for dyslipidaemia treatment, have shown significant reductions in cholesterol levels (5% – 25%). When combined, they may potentially interact synergistically, leading to even greater reductions in cholesterol levels [16].

Poli *et al.* (2018) offer practical indications on the use of cholesterol-lowering nutraceuticals and the identification of individuals who may benefit from treatment. Their study emphasizes that selecting potential candidates should involve a clinical evaluation of cholesterol-lowering needs, a risk/benefit ratio assessment, metabolic profile examination and consideration of patient-specific pathophysiological characteristics [11].

This current study evaluates the efficacy of the food supplement Ateronorm Plus® on the treatment of hypercholesterolaemia. The active ingredients in Ateronorm Plus® are berberine, red yeast rice, naringin, Polygonum cuspidatum, piperine and niacine. These main compounds are briefly described below.

Berberine

Berberine, an alkaloid extracted from the root of *Berberis aristata DC*, has demonstrated a significant efficacy in lowering TC and LDL-C in individuals with dyslipidaemia and lowering Trig. in individuals with diabetes with altered lipid profiles [17]. Berberine achieves these effects primarily by upregulating LDL-receptors (LDL-R) and downregulating proprotein convertase subtilisin/kexin type 9 (PCSK-9) [18]. This mechanism suggests that combining berberine with statins or monacolins can be beneficial as berberine counteracts the negative impact that statins may have on PCSK-9, thereby enhancing their effectiveness [19]. Studies suggest that berberine can reduce LDL-C levels by approximately 10% – 20% [20]. The extract was also subjected to clinical evaluations in individuals with metabolic syndrome. In addition to the

properties mentioned, the extract was found to have anti-diabetic, anti-inflammatory and anti-carcinogenic effects. Thanks to its action on increasing the expression of ATGL (*Adipose Tryglyceride Lipase*), positively associated with weight loss, it also represents one of the possible mechanisms of action in the prevention of obesity [21].

Red yeast rice

Monacolin K and Ka are compounds obtained through the fermentation of rice (*Oryza sativa* L.) by fungi (*Monascus purpureus Went*). Monacolin K shares a similar chemical structure with Lovastatin, a commonly used statin for treating hypercholesterolaemia. Like Lovastatin, monacolin K functions by inhibiting the enzyme HMG-CoA-reductase, which reduces the endogenous synthesis of cholesterol. When taken at a dosage ranging from 3mg to 10mg/day, monacolin K can lead to a significant reduction in LDL-C levels, typically around 20% – 25% [21].

Naringin

Naringin belongs to a subclass of flavonoids called flavanones and is commonly found in various citrus fruits and bergamots. Widely used in the treatment and prevention of obesity, heart disease, diabetes and metabolic syndrome, its hypolipidemic effects include the regulation of lipid digestion, reverse cholesterol transport and LDL receptor expression. Its mechanisms of action include inhibition of HMG-CoA reductase and ACAT. Naringin is also able to activate PPAR-γ and PPAR-α, increasing fatty acids β-oxidation and up-regulating UCP1 (thermogenin) and UCP2 [22]. Naringin is implicated in the modulation of the main pathways associated with the development of obesity and related comorbidities: inflammation, oxidative stress (OS), insulin resistance (IR) and dyslipidaemia. Its role could also extend to the regulation of hunger-satiety mechanisms as it has the potential to modulate the secretion of the hormones involved, such as ghrelin, insulin, adiponectin and leptin. The use of naringin could therefore represent a promising strategy in the treatment of overweight, obesity and related diseases [23].

Polygonum cuspidatum

Water extract of Polygonum cuspidatum contains resveratrol, a polyphenolic compound known for its potential to positively impact lipid metabolism. Resveratrol has been suggested to lower LDL-C and serum lipid levels, inhibit synthesis of Trig. in the liver and reduce hepatic lipid accumulation. However, there is conflicting evidence in scientific literature regarding the effectiveness of resveratrol in improving serum lipid levels, indicating the need for additional studies [24].

Piperine

Piperine is an alkaloid mainly found in black pepper (*Piper nigrum Linn.*) and long pepper (*P. longum*.) Pharmacological properties such as antidiabetic, antidiarrheal, antioxidant, antibacterial, and antiparasitic activities are reported in the literature. Piperine has also been extensively studied as a bioenhancer, for its ability to enhance the effect and bioavailability of orally administered drugs. This is due to various mechanisms such as increased cell membrane permeability, interference with the lipid environment, and inhibition of enzymes involved in drug biotransformation. All of this can lead to better drug absorption and enhancement of their therapeutic effect [25].

Niacin

Niacin, also known as nicotinic acid, has been involved in cardiovascular disease treatment for over 50 years. Treatment with niacin has focused on its favourable actions of increasing HDL cholesterol and reducing LDL and VLDL cholesterol. This potential benefit associated with increasing HDL cholesterol levels has renewed interest in the use of niacin in the treatment of cardiovascular diseases [26].

Materials and methods

Study overview

This observational study analyzed the efficacy profile of 120 days of daily treatment with the nutraceutical supplement Ateronorm Plus® compared with lifestyle interventions alone in a group of individuals affected by moderate dyslipidaemia.

This preliminary work involved dividing 30 participants into two even, randomly appointed groups – treated and control. The 15 participants in the control group took Ateronorm Plus® (one tablet per day) in addition to dietary intervention. All participants were placed on a low-calorie diet with similar calorie restrictions.

In the treated group, the supplement was proposed by some GPs to individuals who showed mild hypercholesterolaemia without the presence of other pathologies. Participants took one tablet per day of Ateronorm Plus® for 120 days. Each tablet contains 500 mg of Berberis aristata extract, 2.8mg of monacolin k (from red yeast rice), 200 mg of naringin, 50 mg of Polygonum cuspidatum extract (of which 0.6 mg resveratrol), 4.9 mg of piperine (from black pepper) and 54 mg of niacin.

Participants

All 30 recruited participants were aged 36 – 72 years and affected by polygenic hypercholesterolaemia. They 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, severe diagnosed pathologies, high or very high CVD risk, severe liver disease, non-pharmacologically controlled thyroid disease, active peptic ulcer, chronic inflammatory bowel disease, pregnancy and breastfeeding, and treatment with lipid-lowering therapy in the 30 days before enrolment.

The average age of participants was 53 ± 10, with a BMI of 29.8 ± 0.54 a 31.5 kg/m^2. The gender balance was 20 men 20 (66.7%) and 10 women (33.3%) respectively. Anthropometric values (such as weight, height and 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. Each participant 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. An unpaired *t*-test was used to verify the effectiveness of the supplement on TC, LDL, HDL and Trig. levels and on anthropometric values (on which the lifestyle interventions have the greatest impact). 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 and GraphPad Prism 9.5.0. The significance level is set at 0.05.

Results

The trial began with 30 participants. All participants finished the course, taking the supplement on at least 90% of the specified days.

At the beginning of the trial, participants at the baseline had the following average values: TC (Ateronorm Plus®: 230 ± 5,61 mg/dL; control group: 232 ± 6.4); LDL (Ateronorm Plus®: 146.1 ± 6.7 mg/dL; control group: 148±7,2); HDL (Ateronorm Plus®: 40.1 ± 2.1 mg/dL; control group: 40.1± 2.5 mg/dL), Trig. (Ateronorm Plus®: 179± 10 mg/dL; control group: 178± 11

mg/dL), weight (Ateronorm Plus®: 89± 0.7 kg; control group: 89.7± 0.7 kg), BMI (Ateronorm Plus®: 29.5± 0.5; control group: 30.2± 0.7).

The average values obtained immediately after the 120 days of treatment were: TC (*t*=10.87; *p*<0.0001); Ateronorm Plus®: 180±6.35, -21.7%; control group: 219±4.91, -5.4%), effect size: 3.97 (huge effect); LDL (*t*=26.08; *p*<0.0001; Ateronorm Plus®: 108±2.1, -26.3%; control group: 146±2.5, -1.6%), effect size: 9.52 (huge effect); HDL (*t*=0.75; *p*=0.46; Ateronorm Plus®: 43±1.8, 9.3%; control group: 42±2.4, 6.3%), effect size: 0.28 (small effect); Trig. (*t*=1.41; *p*=0.17; Ateronorm Plus®: 150±7.5, -16.4%; control group: 157±7.5, -12.2%), effect size: 0.51 (medium effect); weight (*t*=3.55; *p*=0,0013; Ateronorm Plus®: 80.8±1.1, -9.2%; control group: 83.3±1.2, -7.2%); BMI (*t*=2.34; *p*=0,0269; Ateronorm Plus®: 27.5±0.7, -6.9%; control group: 28.3±0.5, -6.1%).

In summary, supplementation with Ateronorm Plus® significantly decreased TC, LDL and Trig. levels in all participants. It is interesting to note that cholesterol levels significantly decreased close to physiological levels. Lifestyle treatment without supplementation with Ateronorm Plus® slightly improved the evaluated parameters and lipid profile, resulting in improvements that were not significant from a clinical point of view. Participants treated with Ateronorm Plus® also obtained advantages in anthropometric values, compared with diet alone. The results are shown in **Fig.1**.

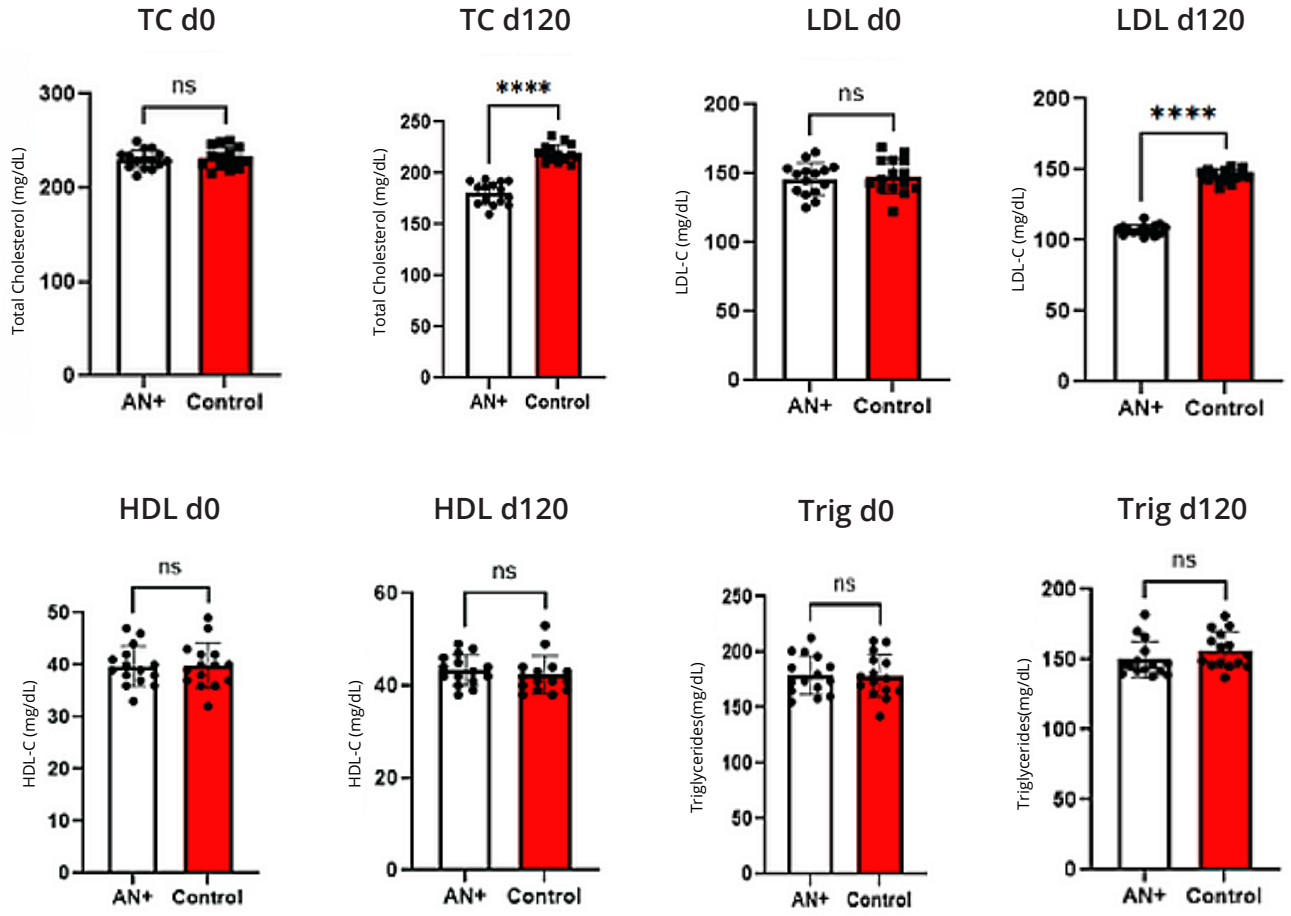

Figure 1: Graphical representation of TC, HDL, Trig. and LDL level at T_0 and T_1.

AN+ = Ateronorm Plus®

Conclusions

Based on the results of the current study, we consider the use of Ateronorm Plus® to be an effective tool for the treatment of non-severe dyslipidaemia, particularly hypercholesterolaemia. In fact, the results showed that Ateronorm Plus® improved serum lipid levels, significantly reducing TC, LDL-C and Trig.

Considering the results on anthropometric parameters such as weight and BMI, the mixture of plant extracts in the nutraceutical supplement Ateronorm Plus® could be useful in improving the metabolic profile of overweight or obese individuals. This could prove critical in assisting and promoting weight loss in individuals undergoing hypocaloric dietary treatment. In addition, when treated and control groups are compared, lifestyle interventions alone appear to be insufficient in improving lipid profiles in individuals with dyslipidaemia.

The nutraceutical supplement Ateronorm Plus® is widely distributed and more easily accessible than prescribed drugs. This could help medium- and long-term compliance among individuals following appropriate counselling on proper usage by physicians, 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

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