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ARTICLE

A Polyphenol-Based Multicomponent Nutraceutical in Dysmetabolism and Oxidative Stress: Results from a Pilot Study

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ABSTRACT

To assess short-term efficacy and safety of a multicomponent nutraceutical (MCN) on dysmetabolism and oxidative stress, a pilot prospective observational study was performed on 21 individuals (12 men and 9 women) who took, for 60 days, 2 tablets per day of an MCN based on antioxidants and metabolism regulators: hydroxytyrosol (15 mg), maqui (300 mg), amla (200 mg), monacolin K (10 mg), berberine (245 mg), astaxanthin (0.5 mg), coenzyme Q10 (100 mg), and folic acid (200 mcg). On day 0 (T0) and day 60 (T60), all participants underwent laboratory tests related to lipid profile, carbohydrate metabolism, oxidative stress, and cellular inflammation. Statistical analysis was applied to the resulting data. A significant improvement of most atherogenesis and oxidative stress biomarkers was recorded (mean figure at T0 and T60, *p* value): total cholesterol 243.50/194.83 mg/dl, *p* = .0002; low-density lipoproteins 174.50/124.58 mg/dl, *p* = .0001; glycemia 96.25/88.50 mg/dl, *p* = .035; total free radicals 306.44/280.93 U.Carr., *p* = .036; serum antioxidant capacity 2103.00/2246.06 $\mu\text{mol/l}$, *p* = .0042; oxidized cholesterol 680.33/597.25 $\mu\text{Eq/l}$, *p* = .0511. Insulinemia, microalbuminuria, high-density lipoproteins, C-reactive protein, and triglycerides had no statistically significant variation. Body weight and systo-diastolic pressure showed no significant change from T0 to T60. No relevant side effects were reported. The investigated MCN (Eonlipid), based on polyphenols, significantly improved the oxidative stress parameters and decreased the majority of atherogenesis parameters at short term. No significant side effects were reported. Further placebo-controlled studies should possibly corroborate the promising results of this pilot study.

KEYWORDS

amla; antioxidants; atherogenesis; hydroxytyrosol; inflammaging; lipid profile; maqui; monacolin K; oxidative stress; polyphenols; free radicals

Introduction

Cardiovascular and neurodegenerative diseases are mostly related to metabolism alterations and to oxidative stress; in fact, atherosclerosis still represents the main cause of death in industrialized countries and a leading cause of disability (Rosamond et al., 2008). Through laboratory testing, it is possible to identify a few specific biomarkers of the altered lipid/glucose profile, of cellular inflammation, and finally of oxidative stress. The possible positive interaction with the main biofactors that play a role in the senescence and

atherogenetic processes may lead to better control of cardiovascular and cerebral degenerative disorders, as well as to healthier aging.

Senescence seems to be related to different possible causal mechanisms (oxidative stress, immunitary/endocrino-senescence, telomere shortening, cellular inflammation, etc.), which interplay a very complex series of processes, resulting in a progressively degenerative sequence of events at the basis of the natural aging of the human organism (de Magalhães, 2013).

Numerous studies have highlighted the importance of proper nutrition and adequate physical exercise to achieve successful aging (de Magalhães, 2013); a specific role has been recognized for dietary supplements as well (de Magalhães, 2013), in order to complement the lifestyle with targeted natural substances that are mostly, but not only, of an antioxidant nature.

A better control of lipid profile alterations may be achieved through statins, as well as through specific phyto supplements, such as polyphenols, which interfere with lipid formation/oxidation (Annuzzi et al., 2014). In fact, low-density lipoproteins (LDL) and oxidized cholesterol probably represent the major independent risk factors for cardiovascular and cerebral diseases (Wald & Thompson, 1994; Nissen et al., 2005; Staprans et al., 2005). Similarly, alterations of glucose metabolism and insulin resistance, with type 2 diabetes onset, contribute to the atherogenetic mechanisms and more generally to the aging process. Polyphenols/antioxidants equally interact positively with carbohydrate metabolism (Dembinska-Kiec, 2008), both reducing insulin resistance, and through other hormetic mechanisms (see the following).

Among polyphenols, a few antioxidants exhibit a higher power against lipid/glucose dysmetabolism: (1) hydroxytyrosol, which is a phenylethanoid (4-2-Hydroxyethyl-1,2-benzenediol) derived from olive leaf, effectively targets different risk factors, achieving evidence-based positive results in cardiovascular, neurodegenerative, and metabolic diseases (Locker, Rowland, & Spencer, 2016; Bullotta, Celano, & Lepore, 2014); (2) maqui (*Aristotelia Chilensis*, Mol.Stuntz), a Chilean berry, has a significant antioxidant power, thanks to its high content of delphinidins, and proven beneficial effects in multiple medical fields (Watson & Schönlau, 2015; Cespeded et al., 2011; Davinelli et al., 2015); (3) amla (*Phyllanthus Emblica*), a plant from the family phyllanthaceae, has clear antidiabetes and lipid-lowering properties (Carlsen et al., 2010; Gopa, Bhatt, & Hemavathi, 2012; Khanna et al., 2015) together with an extremely high antioxidant power, thanks to its high content of tannins; (4) asthaxantin (a keto-carotenoid from the terpenes family), which is derived especially from microalgae, is equally of help in lipid dysmetabolism (Dose et al., 2016). Other herbal remedies such as monacolin K, which is an herbal-derived statin (lovastatin) mostly extracted from red rice (*Monascus Purpureus* Went), and berberine (a quaternary ammonium salt from the protoberberine group of benzylisoquinoline alkaloids), which is usually extracted from the cortex of a plant root (*Berberis Vulgaris* barberry), have clearly shown a positive effect on cholesterol and carbohydrate metabolism (Cicero et al., 2016; Dong et al., 2013). Of interest, lovastatin shares with synthetic statins the possible side effect of creatine phosphokinase (CPK) elevation and rhabdomyolysis, usually at high doses (Cicero et al., 2016).

Most natural principles in the preceding have proved to significantly reduce free radicals and to combat oxidative stress as well. This recovery of the redox balance may help in cardiovascular disease, neurodegenerative diseases, and successful aging more generally (Khurana et al., 2013; Scapagnini, Caruso, & Calabrese, 2010; Sadowska-Bartosz & Bartosz, 2014).

Hyperhomocysteinemia represents another recognized risk factor both for atherothrombotic process and for DNA methylation processes (Stanger et al., 2003). Folic acid (also termed folate, one of the B vitamins) supplementation may counteract this phenotypic pathologic expression of a genetic (MTHFR) mutation.

Table 1. Blood parameters at T0 and T60 and *p* value for the statistical comparison.

	Day 0		Day 60		<i>p</i> value
	Mean	<i>SD</i>	Mean	<i>SD</i>	
Total cholesterol	243.50 mg/dl	30.8	194.8 mg/dl	28.1	.0002
Low-density lipoproteins	174.50 mg/dl	23.92	124.58 mg/dl	18.3	.0001
High-density lipoproteins	51.25 mg/100 ml	10.22	50.33 mg/100 ml	10.25	.48
Triglycerides	116.2 mg/100 ml	60.46	126.4 mg/100 ml	62.17	.39
Oxidized lipoproteins	680.33 uEq/l	148.3	597.25 uEq/l	98.26	.0511
Reactive C protein	4.0 mg/l	6.26	3.1 mg/l	4.37	.19
Glycemia	96.25 mg/dl	5.56	88.50 mg/dl	9.53	.035
Total free radicals	306.44 U.Carr	76.90	280.93 U.Carr	61.68	.036
Serum antioxidant capacity	2103.00 umol/l	223.0	2246.06 umol/l	192.8	.0042
Insulinemia	7.2 uU/ml	2.9	7.8 uU/ml	3.6	.28
Microalbuminuria	6.3 mg/g	3.23	6.4 mg/g	3.46	.92

SD = standard deviation.

In the context of dietary supplements of proven utility in cardiovascular diseases, coenzyme Q10 (Ubidecarenone, Ubiquinone), which is ubiquitous in the human body, primarily in the mitochondria electron transport chain, represents a complementary ingredient when using lipid lowering substances such as monacolin k (Oleck & Ventura, 2016).

A pilot study was conducted to assess any possible benefit and the relative safety from the administration of a multicomponent nutraceutical (MCN) that includes the phyto substances previously mentioned targeting dysmetabolism, oxidative stress, and low-grade chronic cellular inflammation, the latter probably being the common denominator of a quali-quantitatively deteriorated senescence (Franceschi et al., 2000).

Patients and methods

A pilot prospective observational clinical and laboratory study was conducted to assess efficacy and safety of a polyphenol-based MCN with the primary endpoint of improving parameters related to dyslipidemia, glucose metabolism, and oxidative stress. All participants signed an informed consent, and the study was performed in accordance with the principles of the Helsinki declaration.

Inclusion criteria were as follows: in the age range of 30–60 years with body mass index (BMI) up to 35 and with documented signs of dysmetabolism, such as lipid profile or glucose level alterations at blood test, pathologic abdominal circumference, and hypertension.

Exclusion criteria were allergy to one or more of the ingredients of the MCN; active cancer; cardiac/renal/liver insufficiency; ongoing therapy with steroids, lipid-targeting drugs, or anti-inflammatory drugs; or under treatment with hormones, antioxidants, multivitamins.

Initial screening included history taking and physical examination; blood pressure, weight, and BMI were controlled at day 0 (T0) and day 60 (T60).

All participants took two tablets per day of an MCN (Eonlipid) composed of the following active principles, all of them with proved action on metabolism and on oxidative stress (daily dose included): hydroxytyrosol (15 mg), maqui (300 mg), amla (200 mg), monacolin K (10 mg), berberine (245 mg), astaxanthin (0.5 mg), coenzyme Q10 (100 mg), and folic acid (200 mcg).

At T0 and after 60 days (T60) of MCN intake, all participants underwent a series of specific laboratory tests related to lipid profile, carbohydrate metabolism, oxidative stress, and cellular inflammation (Table 1). Blood samples were collected by venipuncture with vacutainer system; all the metabolites were measured on automatic instrumentation (Architect, Abbott

Laboratories). The examined parameters were assessed in plasma fluoride EDTA (glycemia), in urine (microalbuminuria), and on serum (the remaining tests). The following methods were used: hexokinase for glycemia; enzymatic method for lipid profile (e.g., total cholesterol, high-density lipoprotein [HDL], low-density-lipoprotein [LDL], triglycerides); immunoturbidimetry for C-reactive protein; photometry for free radicals and serum antioxidant capacity (SAC); chemiluminescence for insulinemia; immunoturbidimetry for microalbuminuria.

Patients were invited to report any side effect and received oral and written information on the need to maintain a stable lifestyle, without any additional intake of other drugs or supplements with known activity on the investigated parameters.

All data were collected and submitted to the relative statistical analysis by means of PSPP and GraphPad Prism software; p value was calculated for all variables through t -paired test and through Wilcoxon test and a .05 cut-off p value was considered statistically significant for all the investigated variables.

Results

Twenty-one middle-aged participants (12 men and 9 women, mean age 53 years, mean height 171.7 cm, and mean weight 76.5 kg) were prospectively enrolled and there was no patient lost to follow-up; hence, all pre- and postsupplementation data were available for the statistical evaluation.

A remarkable improvement of most laboratory parameters was recorded at two months follow-up, with a statistically significant difference both for values of atherogenesis biomarkers and for oxidative stress parameters. The blood laboratory testing results at T0 and T60 were as follows (mean figure and p value for the comparative statistical analysis) (Table 1): total cholesterol 243.50/194.83 mg/dl, $p = .0002$; low-density lipoproteins (LDL) 174.50/124.58 mg/dl, $p = .0001$; oxidized cholesterol 680.33/597.25 uEq/l, $p = .0511$; glycemia 96.25/88.50 mg/dl, $p = .035$; total free radicals 306.44/280.93 U.Carr., $p = .036$; serum antioxidant capacity (SAC) 2103.00/2246.06 umol/l, $p = .0042$. The other examined parameters did not show a statistically significant variation; more specifically, the T0 and T60 values were respectively as follows: insulinemia 7.2 and 7.8 uU/ml; microalbuminuria 6.3 and 6.4 mg/g; high-density lipoprotein (HDL) 51.20 and 50.4 mg/100 ml; reactive C-protein (RCP) 4.0 and 3.1 mg/l; and triglycerides 103 and 107 mg/100 ml. Figure 1 graphically summarizes the main laboratory outcomes at T0 and T60.

The average body weight and BMI at T0 and T60 were 76.54 kg/25.0 and 76.29 kg/24.9, respectively ($p = .256$), and systolic and diastolic blood pressure remained in the range of normality at T0 and T60, showing no significant variation.

No major side effects were reported by the participants during the study period.

Discussion

Atherogenesis is strictly linked to lipid/glucose dysmetabolism, and oxidative stress and low-grade chronic cellular inflammation negatively interact to initiate and precipitate cardiovascular atherosclerosis and neurodegenerative diseases (Franceschi et al., 2000); all aging processes are similarly and significantly affected by the three negative processes mentioned in the preceding.

Treatment of lipid profile alterations is mostly based on statins, but adherence to lipid-lowering therapy has been questioned for medical (CPK-related) and patient compliance reasons (Vinker et al., 2008). This factual observation may partly explain the growing use

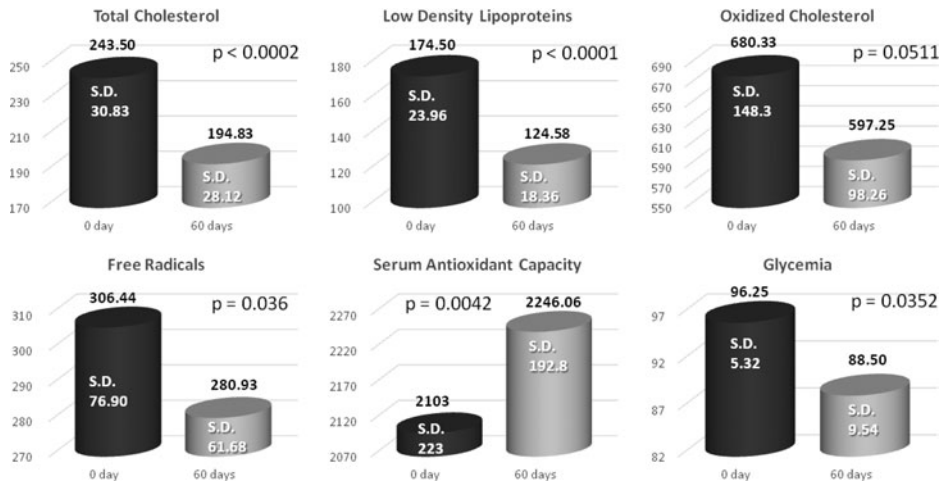


Figure 1. Graphic representation of the main biomarkers.

of natural lipid-lowering substances to improve patient compliance and possibly bypass the adverse effects of statins.

Nutraceuticals have increasingly become popular in different medical fields, such as cardiovascular and neurodegenerative diseases, as well as in longevity medicine. Studies on nutraceuticals have shown contrasting evidence in terms of regulation of lipid metabolism (Annuzzi et al., 2014; Locker et al., 2016; Bullotta et al., 2014; Watson & Schönlaui, 2015; Khanna et al., 2015; Verhoeven et al., 2015; Scicchitano et al., 2014). Most positive outcomes from trials on nutraceuticals in neurocardiovascular diseases have been highlighted when employing polyphenols. Namely, hydroxytyrosol, maqui, and amla have shown an interesting lipid/glucose-lowering effect in a few recent studies and literature reviews (Locker et al., 2016; Bullotta et al., 2014; Watson & Schönlaui, 2015; Gopa, Bhatt, & Hemavathi, 2012; Khanna et al., 2015; Verhoeven et al., 2015), while in the last decade it has been shown how monacolin k and berberine may be effective in improving atherosclerosis processes (Cicero et al., 2016; Dong et al., 2013; Verhoeven et al., 2015; Scicchitano et al., 2014).

By means of antioxidants, it is possible to contrast oxidative stress and excessive production of free radicals; this validated approach has been promoted in several medical fields and more in general in longevity medicine (De Magalhães, 2013; Sadowska-Bartoszk & Bartoszk, 2014).

Regarding the literature data presented in the preceding, the natural principles contained in the investigated MCN (namely maqui, hydroxytyrosol, amla, monacolin K, asthaxantin, and berberine) have been shown to potentially achieve interesting results in individuals affected by hyperdyslipidemia, diabetes, metabolic syndrome, and other dysmetabolisms.

The promising outcomes of our prospective observational study highlight the benefit of this polyphenol-based MCN intake on (1) a few factors related to atherogenesis, such as lipid profile alterations, hypertension, glucose metabolism; (2) metabolic alterations; (3) oxidative stress; and (4) low-grade chronic cellular inflammation (at the basis of the so called “inflammaging”). It is possible to speculate that the synergistic action of multiple powerful antioxidants (maqui, hydroxytyrosol, and amla primarily), together with the proven anticholesterol and glucose-control properties of monacolin K and berberine, has probably increased the positive influence of each phyto ingredient on the investigated metabolism variables. Similarly, the presence of folic acid in the investigated MCN may have added the antihyperhomocysteinemia action; on the other side, coenzyme Q10 may have been of help with its “protective”

action from any possible muscular interference of monacolin K, which may explain the absence of any specific muscular (CPK increase-related) symptoms in our patients.

The figures of oxidized cholesterol and LDL were significantly reduced after 60 days of MCN supplementation, which accounts for the double-directed action both on the lipid profile and on the lipid oxidation; these two components probably represent (much more than total cholesterol) the most important biomarkers in atherosclerosis laboratory screening. The possible relationship between our outcomes and the proposed phyto-approach supplementation in this study may be due to the targeting of both these factors.

The remarkable decrease of free radicals and increase of SAC in our participants proves an overall significant action of the tested MCN on the oxidative stress, hence on low-grade chronic cellular inflammation and all related degenerative senescence processes.

Intuitively, one would expect that the overall benefit of the tested MCN on the majority of the investigated blood parameters could have been more pronounced in a cohort of patients with more relevant metabolic alterations; similarly, a longer-lasting supplementation could have resulted in a wider range of improved biomarkers.

The patients reported no specific adverse event, and main anthropomorphic parameters (weight/BMI, blood pressure) remained unchanged throughout the study period.

Literature data on the possible role of a few polyphenols as hormetins (Son, Camandola, and Mattson, 2008; Calabrese et al., 2012) refer to their feature to activate the so-called hormesis effect. Hormesis is a biological phenomenon in which a beneficial effect (improved health, stress tolerance, longevity) derives from the exposure to low doses of an agent that is toxic, or even lethal, at higher doses (Calabrese et al., 2015). The hormesis beneficial contribution to human health is mostly mediated through specific vitagene activation, mammalian target of rapamycin (mTOR) inhibition, autophagy induction, and sirtuin activation. (Calabrese et al., 2012). This specific and relevant feature of a few antioxidants may explain furthermore the holistic positive action of the MCN in our participants, which could be, at least partially, mediated through the possible hormesis activation phenomenon.

In conclusion, a positive relationship was observed between the administration of the investigated MCN and the measured endpoints. The phytochemistry-based nutraceutical showed a good efficacy profile at short term in our cohort of patients concerning dysmetabolic profile and oxidative stress.

The reported data present a few limitations, which may be overcome by a future larger randomized controlled trial. As this cohort study focuses on a small group of patients, further research is needed to validate these promising, but preliminary, results. The investigated sample of patients presents demographic figures that may be different from those typically encountered in the literature that pertains to metabolic syndrome and the aging processes. The real efficacy and safety of the tested MCN in patients affected by significant dysmetabolism and oxidative stress may be confirmed through further data to possibly corroborate the outcomes of our pilot study.

Conclusion

Daily intake of two tablets of the investigated MCN (Eonlipid) has resulted in a significant improvement of the antioxidant defenses and a statistically significant reduction of free radicals and of most atherogenesis parameters in general. No significant side effects were reported. This study elicited the possible beneficial effect of a polyphenol-based multicomponent nutraceutical on a few factors related to cardiovascular and neurodegeneration, as well as on the aging process.

Future studies with a placebo group and on a wider sample of patients are required to possibly confirm the promising results of this preliminary study.

Declaration of interest

The authors have no potential conflict of interest that pertains to this article. Proeon srl provided all participants with the MCN Eonlipid free of charge; Proeon srl did not interfere with data collection, data analysis, or text compilation. No grant was provided from Proeon srl for the performance of the study.

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