A Randomized Clinical Trial Evaluating the Efficacy of an Anthocyanin–Maqui Berry Extract (Delphinol®) on Oxidative Stress Biomarkers

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Key words: berry, anthocyanin, oxidative stress, oxidized LDL, F_2-isoprostanes

Objective: Berries are a rich source of anthocyanins, and clinical data suggest that a polyphenol-rich diet may exert health-promoting effects by reducing oxidative stress. The aim of this study was to elucidate the effects of dietary supplementation with Delphinol (trademark owned by MNL Chile) standardized maqui berry (*Aristotelia chilensis*) extract on products of lipid peroxidation in healthy, overweight, and smoker subjects.

Methods: In a double-blind, placebo-controlled design, 42 participants (age 45–65 years) consumed in random order either a standardized extract of maqui berry (162 mg anthocyanins) or a matched placebo, given 3 times daily for 4 weeks. The samples were collected at baseline, after the end of the supplementation, and 40 days after the end of the study. Primary outcome was the measure of oxidized low-density lipoprotein (Ox-LDL) and F_2-isoprostanes in plasma and urine, respectively. Secondary outcomes included anthropometric measures, blood pressure, and lipid profile.

Results: Delphinol supplementation was associated with reduced levels of Ox-LDL in the anthocyanin group compared to baseline ($p < 0.05$). There was also a decrease in urinary F_2-isoprostanes (8-iso-prostaglandin F2α) at 4 weeks versus baseline in the Delphinol-supplemented group ($p < 0.05$). However, no differences in primary outcomes were evident at 40 days of follow-up. In the fourth week of the intervention, no significant differences were noted for anthropometric characteristics, ambulatory blood pressure, and lipid profile.

Conclusions: Our observations suggest that dietary interventions with maqui berry extract may improve oxidative status (Ox-LDL and F_2-isoprostanes) in healthy adults, overweight adults, and adult smokers.

INTRODUCTION

Growing clinical studies suggest that the consumption of polyphenol-rich foods or polyphenol extracts may attenuate oxidative stress and chronic inflammatory status associated with noncommunicable diseases (NCDs) [1,2]. Polyphenols are a multitude of bioactive compounds that typically occur in plant-based foods. Among polyphenols, anthocyanins, a large group belonging to the flavonoid family, have shown to modulate a variety of biochemical/signaling pathways involved in promoting beneficial properties, including vasculoprotective effects, cognitive enhancement, improvement in muscular performance, and anticancer activities [3–6]. Anthocyanins, glycosides of anthocyanidins, are responsible for the colors displayed by many frutis and are widely distributed in berries. These natural nontoxic pigments are water-soluble compounds and divided into 6 classes: malvidin, delphinidin, petunidin, pelargonidin, cyanidin, and peonidin [7]. The position and number of the hydroxyl and methyl groups in the skeleton are crucial for the radical scavenging activities of anthocyanins, and delphinidin containing 3 hydroxylation in the B ring showed the highest antioxidant activity [7,8]. Although *in vitro* evidence strongly supports a role of anthocyanins in the modulation

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of well-defined molecular targets considered to be useful for the prevention of NCDs [9–11], the few human intervention studies offer conflicting and inconclusive results [12–14]. Because berry composition depends on genetic, seasonal, and postharvest factors, interspecies variation in anthocyanin content and different metabolic fates in human metabolism may partially explain the variability in clinical study results. *Aristotelia chilensis* (Molina) Stuntz, also known as maqui, is a plant of the Elaeocarpaceae family that grows in southern Chile (Valdivian temperate rain forest). In the traditional native herbal medicine, maqui berry juices have long been used for medicinal purposes, and several studies showed a peculiar phytochemical composition of maqui berry with high anthocyanin content (137.6 ± 0.4 mg/100 g fresh weight) and a relatively high percentage constituted by delphinidin (34% of total anthocyanins) [15,16]. Oxidative stress and redox state unbalance are common underlying mechanisms of several NCDs [17], and anthocyanins may represent a relevant nutritional approach to prevent oxidative modification of proteins and lipids. Therefore, the aim of this short-term dietary intervention trial was to assess the antioxidant effects of an anthocyanin-rich extract in healthy, overweight, and smoker subjects.

METHODS

Subjects

Fifty overweight volunteer smokers were recruited from the Inter-University Consortium "SannioTech", Benevento, Italy. The participants were enrolled into this clinical trial (recruiting and follow-up) between January 2014 and April 2014. This study was approved by the local ethics committee (Independent Ethics Committee of the Hospital "Gaetano Rummo" Benevento ASL BN 1 clinical protocol no. R.F. Rev1-10292014). All investigated subjects gave their informed written consent. All procedures were in accordance with institutional guidelines and were carried out in compliance with the Declaration of Helsinki. The health status of the participants was assessed and they were selected according to the following inclusion criteria: light smokers (<1 pack per day), inclusive age 45–65 years, good general health, and body mass index between 25 and 30 kg/m^2. Table 1 shows the baseline characteristics of the participants. None of the subjects had a history of chronic diseases. Exclusion criteria included individuals who were taking anti-inflammatory drugs, cardiovascular medications, lipid-altering drugs, and hormone replacement therapy. We also excluded individuals engaged in vigorous exercise (>2 × 30 min/week), vegetarians, and people who routinely took multivitamins or herbal supplements. The participants were instructed to maintain their usual dietary intakes.

Intervention Study Design

The study was a randomized, double-blind, placebo-controlled trial with a 40-day follow-up period. According to the specific inclusion criteria, 42 subjects were deemed eligible for the study (Fig. 1). The subjects were randomly assigned to either the anthocyanin group ($n = 16$; 11 men and 5 women) or the placebo group ($n = 26$; 18 men and 8 women). Investigators and participants were blinded to anthocyanin group identity until after completion of the data analysis. The treatment period lasted for 4 weeks and the anthocyanin group was instructed to consume 3 capsules of 150 mg standardized maqui berry extract containing 54 mg of anthocyanins (Enervit S.p.A, Milano, Italy) daily, for a total intake of 162 mg anthocyanins/day. The placebo group received identical placebo capsules 3 times daily for 4 weeks. The samples were collected at baseline, at the end of the intervention period, and 40 days after the end of the treatment. All subjects declared that they did not change their diets during the course of the

Table 1. Anthropometric Characteristics and Blood Lipid Profile from Baseline to Follow-up[a]

	Placebo ($n = 16$)			Delphinol® Treatment ($n = 26$)			
	Baseline	4 weeks	Follow up	Baseline	4 weeks	Follow up	*P*
Weight (kg)	79.5 ≠ 14.8	79.5 ≠ 14.9	79.6 ≠ 14 8	78.8 ≠ 14.3	79.3 ≠ 14.4	79.7 ≠ 14.1	NS
BMI (kg/m^2)	28.5 ≠ 4.7	28.3 ≠ 4.6	28.2 ≠ 4.8	28.9 ≠ 4.1	29.5 ≠ 4.9	29.9 ≠ 4.7	NS
Waist (cm)	100.6 ≠ 9.1	100.3 ≠ 9.3	100.4 ≠ 9.3	99.7 ≠ 9.5	100.3 ≠ 9 1	98.2 ≠ 9.7	NS
SBP(mm Hg)	128.5 ≠ 22.2	129.1 ≠ 23.1	128.7 ≠ 20.5	127.8 ≠ 21.2	130.2 ≠ 22.2	129.8 ≠ 21.6	NS
DBP(mm Hg)	81.4 ≠ 12.1	81.3 ≠ 13.5	79.8 ≠ 14.3	82.2 ≠ 12.5	82.8 ≠ 12.6	83.5 ≠ 13.6	NS
TG (mmol/L)	1.35 ≠ 0.98	8.37 ≠ 0.56	1.33 ≠ 0.78	1.33 ≠ 0.66	1.29 ≠ 0.86	1. 30 ≠ 0.94	NS
TC (mmol/L)	4.35 ≠ 0.45	4.32 ≠ 0 66	4.36 ≠ 0.84	4.34 ≠ 0 55	4.33 ≠ 0.97	4.33 ≠ 0.83	NS
HDLc (mmol/L)	1.16 ≠ 0.31	1.15 ≠ 0.27	1.15 ≠ 0.76	1 16 ≠ 0.35	1. 17 ≠ 0.47	1 16 ≠ 0.32	NS
LDLc (mmol/L)	2.75 ≠ 0.88	2.73 ≠ 0.76	2.73 ≠ 0.93	2.74 ≠ 0.97	2.72 ≠ 0.75	2.72 ≠ 0.79	NS

BMI = body mass index, SBP = systolic blood pressure, DBP = diastolic blood pressure, TG = triglycerides, TC = total cholesterol, HDLc = high-density lipoprotein cholesterol, LDLc = low-density lipoprotein cholesterol.

[a]All values are mean ± SD. There were no significant differences. Significance was set at $p > 0.05$.

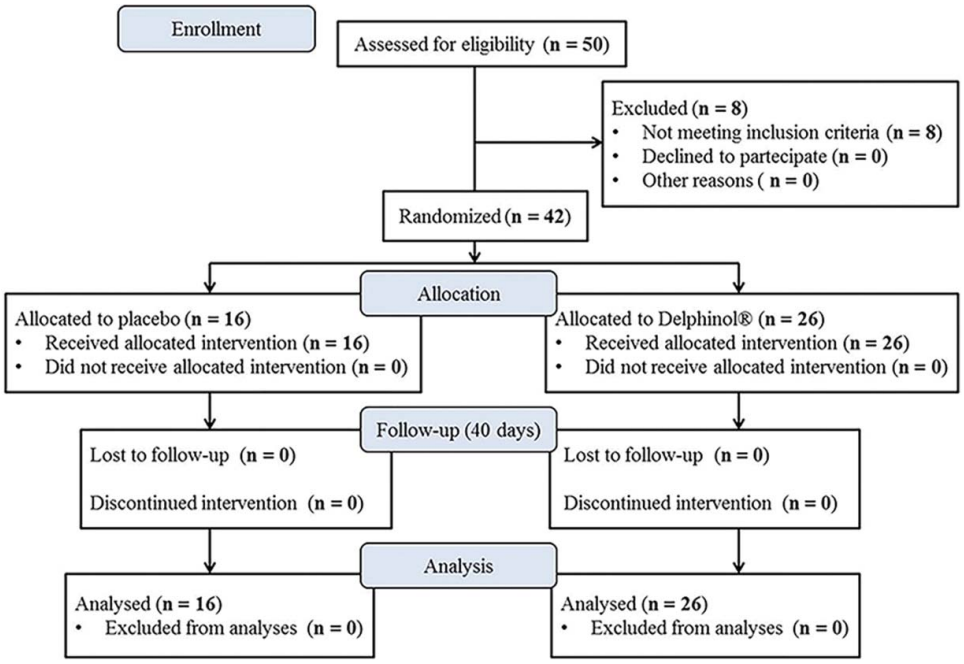

Fig. 1. Flowchart of enrollment, intervention allocation, and follow-up.

study and they attended our medical facility every month to assess clinical conditions and adherence to the protocol.

Material

The anthocyanin and placebo capsules used in this trial were identically packaged. According to the manufacturer (Enervit S.p.A), Delphinol maqui berry extract is standardized to contain approximately 35% of total anthocyanins and 28% of total delphinidins. These capsules also contained maltodextrin to maintain stability, as well as traces of dietary minerals, such as calcium and magnesium. Placebo capsules consisted of maltodextrin. The dose of anthocyanins was determined based on 2 recent human studies. The first clinical investigation performed by Karlsen et al. [11] found that daily intake of 320 mg anthocyanins is safe and effective against inflammatory response. The second study reported that the administration of 200 mg Delphinol has no side effects [18].

Biochemical Analyses

Samples were collected in EDTA-containing vials that were immediately stored at −80°C until analysis. Triglycerides, total cholesterol, high-density lipoprotein cholesterol (HDLc), and low-density lipoprotein cholesterol (LDLc) were measured using colorimetric enzymatic tests (Thermo Scientific, Waltham, MA). The plasma concentration of oxidized LDL (Ox-LDL) was measured by a sandwich enzyme-linked immunosorbent assay methodusing a commercially available kit (Immundiagnostik AG, Bensheim, Germany) described previously by Licastro et al. [19].

Determination of Urinary F_2-Isoprostanes

According to the study design, sampling of morning urine was performed at the beginning (baseline), at 4 weeks, and at the end of follow-up. Urine samples were collected into 10-ml plastic centrifuge tubes (FL Medical, Torreglia, Italy) and stored at −80°C until analysis. 8-iso-Prostaglandin (PG) F2α in urine was determined by liquid chromatography–tandem mass spectrometry (LC-MS/MS) as previously described by Yan et al. [20] with slight modifications. Briefly, 1 mL urine was spiked with deuterated internal standards (8-iso-PGF2α-d4; 20 ng/ml) and the supernatant was loaded on a C18 solid-phase extraction cartridge (SPE C18; Supelco, Bellefonte, PA) that had been preconditioned with 5 ml of methanol and equilibrated with 5 ml of water. The cartridge was washed successively with 5 ml of water, 5 ml ethanol : water 5:95, and 1 ml of hexane. SPE C18 cartridges were eluted with 2 ml of ethyl acetate and dried under a stream of nitrogen. After adding 50 μl of acetonitrile : water 80:20 to the eluent, the samples were analyzed using an LCMS-8040 LC-MS/MS system (Shimadzu, Kyoto, Japan). Data are presented as picograms of 8-iso-PGF2α per milligram of urinary creatinine. Creatinine in urine was measured with a spectrophotometric method using a clinical chemistry analyzer (BPC Biosed, Castelnuovo di Porto, Italy). Overall recovery of the method was over 80%.

Statistical Analysis

The data are expressed as mean ± SD. The differences between groups were evaluated by *t* test for independent samples and by analysis of variance. In each group, differences

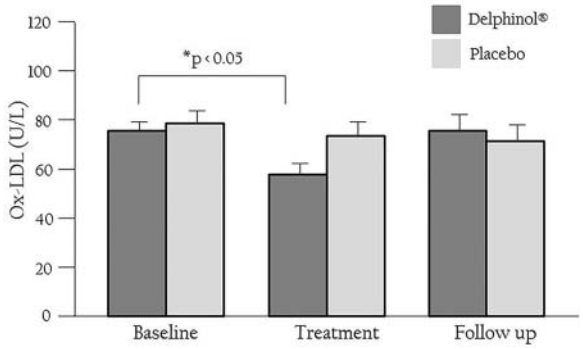

Fig. 2. Change in Ox-LDL values within each group after 4 weeks of intervention and 40 days of follow-up. Data are expressed as mean ± SD. *Significantly different from baseline at $p < 0.05$.

from baseline were evaluated by *t* test for paired samples. Statistical significance was assigned as $p < 0.05$. Statistical analyses were performed using R statistical Software (Revolution Analytics, Palo Alto, CA).

RESULTS

From the initial 50 subjects enrolled in the study, 42 met the inclusion criteria and were randomized into the trial (Fig. 1). The participants were in general healthy and no adverse events resulting from the consumption of either the placebo or anthocyanin capsules were observed throughout the intervention. Baseline characteristics of the participants are detailed in Table 1. From baseline to follow-up, there were no statistical differences among the different groups in anthropometric measurements, blood pressure, and lipid profile (except Ox-LDL; Table 1). Although total cholesterol, triglycerides, HDLc, and LDLc levels were unaffected by Delphinol treatment, after 4 weeks of intervention, maqui berry extract supplementation resulted in decreased plasma concentration of Ox-LDL in the Delphinol group compared to baseline (Fig. 2, $p < 0.05$). However, no significant differences in plasma concentration of Ox-LDL were observed between the placebo and supplemented groups after the 40 days of follow-up compared to the levels of Ox-LDL at baseline and at the end of the intervention period. Taken together, these results show that an anthocyanin-rich diet may reduce oxidative modifications of LDL in overweight and smoker subjects. In an effort to further explore the antioxidant impact of Delphinol supplementation, we examined the urinary excretion of 8-iso-PGF2α. As shown in Fig. 3, 8-iso-PGF2α did not differ at baseline between the placebo and Delphinol groups. Following 4 weeks of Delphinol consumption, a significant decrease in urinary 8-iso-PGF2α levels was observed in the supplemented group (Fig. 3, $p < 0.05$). In contrast, at the end of follow-up period, no statistically significant changes were noted in 8-iso-PGF2α concentrations in either group. These data raise the possibility that Delphinol supplementation may be an effective nutritional strategy to counteract oxidative challenge.

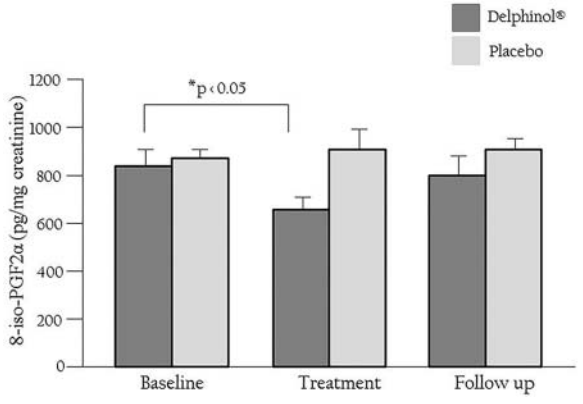

Fig. 3. Effects of Delphinol supplementation on urinary excretion of 8-iso-PGF2α in overweight smokers. Data are expressed as mean ± SD. *Significantly different from baseline at $p < 0.05$.

DISCUSSION

An extensive body of evidence suggests that oxidative stress and resulting lipid peroxidation may be crucial in the pathophysiology of several diseases [21–23]. The beneficial effects of berry fruits on oxidative stress have been investigated in different experimental *in vitro* and *in vivo* studies [24]. Berry anthocyanins have attracted scientific attention for their antioxidant and anti-inflammatory activities [25] and in this context it should be pointed out that maqui berries have higher anthocyanin content than other Chilean berries [26]. This study was designed to investigate whether consumption of maqui berry extract is effective in reducing lipid peroxidation products. In particular, the rationale behind this study was to assess whether specific anthocyanin derivative(s) present in maqui berry extract, such as delphinidin, can improve oxidative status.

With regard to secondary outcomes, we observed no effect of maqui berry supplementation on blood pressure and anthropometric variables. In addition, no significant effects were seen on total cholesterol, triglycerides, HDLc, and LDLc levels (Table 1). These results contrast with other published studies in which anthocyanin supplementation improved lipid panel indices [14,27,28]. Although there is much evidence on the lipid-lowering effects of anthocyanins, the discrepancy may be attributed, at least partly, to different characteristics of the enrolled subjects and diversity of anthocyanin composition and dosage of berry extracts. However, in the current study the decrease in concentration of Ox-LDL, after a short period of supplementation with maqui berry extract (Fig. 2), may indicate that this dietary supplement improves oxidative stress in healthy humans. These findings are consistent with previous

reports indicating that diets rich in anthocyanins can reduce Ox-LDL [29,30]. The use of urine samples (free from lipids) to evaluate 8-iso-PGF2α levels was based on evidence from clinical trials suggesting that Ox-LDL and 8-iso-PGF2α represent different entities in the process of oxidative modification [31,32]. Thus, the present study used 8-iso-PGF2α as a urinary index of oxidative stress. Previous reports have shown that the urinary excretion of 8-iso-PGF2α is enhanced under several conditions, including cigarette smoking [33,34]. In agreement with other antioxidant supplementation trials [35,36], we have shown a decrease in urinary 8-iso-PGF2α in overweight smokers (Fig. 3). This result suggests that the effect of Delphinol on 8-iso-PGF2α is both rapid and sustained throughout the intervention. However, although anthocyanin supplementation produced a reduction in the concentration of Ox-LDL and 8-iso-PGF2α, the values returned to baseline after 40 days of follow-up. Taken together, these data raise the possibility that Delphinol may induce a positive and transient systemic effect on oxidative status. However, there are several limitations to be acknowledged in the present study, most important of which is the absence of a prescribed standardized diet. Therefore, the findings must be viewed with caution and we need to confirm the present results in the setting of a controlled feeding study. Delphinol was consumed for a short period of time, and it remains unclear whether the beneficial effects on oxidative stress would persist with longer treatment. Furthermore, our study provides no insight into the mechanism of benefit, and additional studies are needed to define the mechanisms of these effects. The study limitations were balanced by the placebo-controlled design and a relatively large sample size. In conclusion, our results indicate that dietary supplementation with maqui berry extract exerts antioxidant effects in healthy, overweight, and smoker subjects. Overall, this study suggests a positive nutritional influence of anthocyanin on lipid peroxidation, and this effect may be considered useful for the prevention of diseases associated with oxidative stress.

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