SAPHENOUS SPARING TREATMENTS ORIGINAL ARTICLE

Efficacy and safety of a Maqui berry-based nutraceutical in venous insufficiency of the lower limbs

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Abstract Aims: to assess effectiveness of supplementation with a nutraceutical containing an extract of Maqui berry on symptoms and signs of patients with venous insufficiency of the lower limbs

Patients and methods: a preliminary prospective cohort clinical and instrumental study was performed in a single center, on patients affected by venous insufficiency of the lower limbs related to varicose veins, C2-C4 of CEAP classification. All patients were prospectively enrolled and investigated for a two-month period and they took 2 tablets a day of a nutraceutical containing 500 mg of Maqui berry extract. Venous symptom assessment with visual analogue scale (VAS) was performed at T0 (baseline), T1 (30 days after T0) and T2 (60 days after T0). Short-form 12 questionnaire (SF12) for mental and physical condition was compiled at T0 and T2. Both blood C-reactive protein (CRP) and edema measurement in the lower leg (through circumferences and derived volumetry) were performed at T0 and T2. Compression stockings were allowed if previously used at least one month before T0. Maintenance of the previous lifestyle and nutrition was required throughout the study duration. Student's test for paired data was used for statistical analysis.

Results: a cohort of 45 patients, 35 females and 10 males, mean age 56.4 ± 1,7, with an average body mass index of 26.5 ± 0,5, were investigated. At T0 CEAP C distribution was: 5 C2, 31 C3, 9 C4. No patient was lost to follow-up. VAS assessment showed a statistically significant ($p < 0.0001$) improvement of all symptoms; mean value of heaviness, pain, swelling sensation and dysesthesia at T0 and T2 (T2/T0) were 8.8/5.3, 7.6/4.2, 8.7/5.5 and 6.3/3.3 respectively. The mental component of SF12 improved from 23.2 to 37.0 ($p<0.0001$), whereas the physical component did not show any relevant variation. CRP was statistically ($p<0.01$) lower at T2. Lower leg mean volumetry did not show any significant variation between T0 and T2, though ankle circumference decreased of 2 mm. No side effects were reported.

Conclusions: in this preliminary prospective cohort study the nutraceutical Maqui 500® proved to be effective and safe in patients affected by venous insufficiency of the lower limbs. A statistically significant improvement of venous symptoms, CRP and SF12 mental score was demonstrated in this clinical series; a lower though non-significant effect on edema was found. Larger cohort, randomized studies may possibly corroborate the outcomes of this preliminary study.

Keywords maqui, chronic venous disease, polyphenols, inflammation, oxidative stress

Introduction

Chronic venous disease (CVD) of the lower limbs is a common disease which spans from teleangiectasias (C1 of CEAP classification) to active venous ulcer (C6). Epidemiology of CVD includes a 20-64% incidence of varicose veins, a 5% cumulative incidence of C3-C6 patients and, lastly, the patients with active or healed ulcers (C5 and C6) are estimated to be about 1-2% of the general population[1]. These numbers may describe in an approximate way the relevant socio- economic costs CVD may generate worldwide

Ambulatory venous hypertension and microcirculation stasis are the basic trigger mechanisms of the related venous symptoms and signs in the lower limbs[1].

Similarly, lymphatic drainage is strictly connected to venous function as to the recovery of macromolecules and fluids from the tissues[2], hence CVD may result in a series of alterations of the microcirculation/tissue homeodynamics.

From the biochemical point of view inflammation, oxidative stress and hypoxia represent the core mechanisms of any clinical expression of CVD[1,3,4]. Basically, the overexpression of several pro-inflammatory cellular/cytokine pathways has been described in several publications regarding tissues affected by CVD; furthermore, free radical accumulation characterizes cell metabolism in presence of varices, post-thrombotic syndrome, venous ulcers, lymph stasis and other related diseases[1, 3-6].

CVD may progressively lead to several symptoms and signs which may affect patient's quality of life with a repercussion on the general physical and mental components. Therapy of CVD is based also upon conservative measures, such as compression, drugs (anticoagulants, venotropics, etc.), and nutraceuticals. Venoactive compounds address venolymphatic microcirculation and bioflavonoids are the most referenced active principles in the pertinent literature[7-9].

Anthocyanins represent the most relevant part of bioflavonoids, as to their action on venous diseases, and delphinidins, which in turn represent the most active compounds within anthocyanins, were shown to exert a remarkable anti-oxidant/anti-inflammatory activity, together with an antithrombotic action[10], on artero-venous capillaries[11,12]

Maqui berry (*Aristotelia Chilensis*) has been found to be one of the richest fruits in terms of anthocyanins and of antioxidant power, due to its very high content of delphinidins[13,14].

Maqui-based food supplements have been tested with interesting results in oxidative stress and inflammation[15,16]; similarly, a few studies have documented some maqui efficacy on cardiovascular/metabolic diseases[16-21].

In the present preliminary study, a maqui-based nutraceutical has been investigated in patients with CVD. The potential multi-targeting action of this polyphenol-based compound (anti-oxidant, anti-inflammatory, microcirculation-protective) has been assessed in patients with varicose veins and related symptoms, testing its efficacy and safety at short-term from the clinical and experimental points of view.

Patients and Methods

A prospective cohort clinical and instrumental study was performed in a single center. The inclusion criteria were: symptomatic patients affected by CVD related to varicose veins, C2-C4 of CEAP classification, wearing elastic stockings from at least one month before the start of the study. Exclusion criteria were: acute deep/superficial vein thrombosis or dermatolymphangioadenitis, ongoing treatment with venotropic drugs, diuretics, or with any other potentially edema-generating drug (e.g. corticoids, calcium-blockers etc.), active cancer, cardiac-renal-liver failure, body mass index (BMI) above 35. All patients were prospectively enrolled (on an intention-to-treat basis) and investigated for a two-month period; they took 2 tablets a day (before breakfast and before lunch) of a maqui berry-based nutraceutical (Maqui 500 ®, Proeon). Each tablet of the nutraceutical contained 500 mg of Maqui berry lyophilized extract, with an antioxidant power of 70000 µmol TE / 100g as to the oxygen radical absorbance capacity (ORAC).

The following vein-related symptoms of both lower limbs were assessed through visual analogue score (VAS) system: heaviness, pain, paraesthesias/ dysaesthesias, itching, swelling sensation; diuresis was scored in a similar manner as well. The 0 (no symptoms)-to-10 (maximal symptom intensity) scoring modality was referred for each symptom by patients at the baseline, just before the start of the intake of the nutraceutical (T0), 30 days (T1) and 60 days (T2) after T0. Daily diuresis was qualitatively scored by the subjects as 10 when the quantity of urine per day was generally very low; conversely, 0 score indicated a high quantity of daily urine; the comparison between T2 and T0 permitted the subjects to score the possibly different diuresis as consequence. No quantitative measures were used for this parameter.

Short-form 12 questionnaire (SF12), a validated tool to assess mental and physical condition, was compiled by patients at T0 and T2. Blood C-reactive protein (CRP), which is a reliable general biomarker of inflammation, was assessed at T0 and T2. Similarly, edema measurement in the lower leg (through circumferences and derived volumetry) was performed in both legs at T0 and T2. More in detail, volume changes were calculated through the pre-post-therapy tape measurement of the circumferences of the lower leg every 8 cm, starting from medial malleolus salience, for a total of four circumferences. The lower leg volumetry then resulted from the following truncated cone ("frustum method") formula:

Volume of each segment of truncated cone

$$\frac{h\ \ (C_1 \times C_1 + C_1 \times C_2 + C_2 \times C_2)}{12\ \ \pi};$$

In the formula above C1 is the most distal circumference (i.e. at the malleolar level), C2 is the circumference immediately above C1 and π is the fixed value of 3,14. The summation of the three single truncated cone volumes gives the total volume of the lower leg (below the knee leg volume). The mean value between the volumes of the two lower legs was calculated for each patient, and it was included in the database for the final data analysis.

Maintenance of the previous lifestyle and nutrition was required throughout the study duration. Student's test for paired data was used for statistical analysis of the collected data, using Excel ®, Microsoft, software. A 0.05 cut-off p-value was considered as statistically significant for all the investigated variables.

Patients were requested to report about any adverse event throughout the treatment period. BMI was calculated at T0 and T2 , so to assess any significant patient's increase/ decrease in weight which might bias the final outcomes.

MAIN OUTCOMES AND STATISTICAL ANALYSIS AT T0 AND T2											
VARIABLE	$\underline{x}_{T0}$	s_{T0}	$\underline{s}_{T0}$	$\underline{x}_{T2}$	s_{T2}	$\underline{s}_{T2}$	$\underline{\Delta x}$	$s_{\underline{\Delta x}}$	$\underline{s}_{\Delta x}$	t	p
VOLUMETRY	3040	553	80	3060	546	80	21	113.89	17	1.3	n.s.
ANKLE CIRCUMFERENCE	24.9	3.0	0.4	24.7	3.05	0.5	-0.19	0.27	0.04	4.7	<0.001
Heaviness	8.8	1.76	0.3	5.3	1.38	0.2	-3.4	1.47	0.2	15.6	<0.001
Pain	7.6	2.95	0.4	4.2	1.65	0.2	-3.4	1.22	0.2	10.4	<0.001
Swelling	8.7	1.58	0.2	5.5	1.65	0.2	-3.2	1.66	0.2	12.9	<0.001
Dysesthesia/ Paresthesia	6.3	2.97	0.4	3.3	2.11	0.3	-3.0	1.86	0.3	10.9	<0.001
Itch	6.0	4.30	0.6	2.9	2.48	0.4	-3.1	2.92	0.4	7.1	<0.001
Diuresis	3.2	2.86	0.4	2.4	2.47	0.4	-0.82	1.17	0.17	4.7	<0.001
Physical Score	43.1	4.21	0.6	43.1	3.98	0.6	0.0	2.82	0.4	0.0	n.s.
Mental Score	23.21	1.1	0.17	37	7	1	14	6.7	1	13.7	<0.001
CRP	2.8	2.19	0.3	2.6	2.09	0.3	-0.14	0.20	0.03	4.7	<0.001

Table I Summary of the outcomes regarding all the investigated parameters, including the statistical analysis for each variable:

$\underline{x}_{T0}, \underline{x}_{T2}, and\ \underline{\Delta x}$ - the mean at time T0 and T2 and of their difference;

$s_{T0}, s_{T2}, and\ s_{\underline{\Delta x}}$ – the standard deviation at time T0 and T2 and of their difference;

$\underline{s}_{T0}, \underline{s}_{T2}, and\ \underline{s}_{\underline{\Delta x}}$ – the standard error of the mean at time T0 and T2 and of their difference;

t - the absolute value of mean difference divided by the standard error of the mean.

All variables have 44 degrees of freedom.

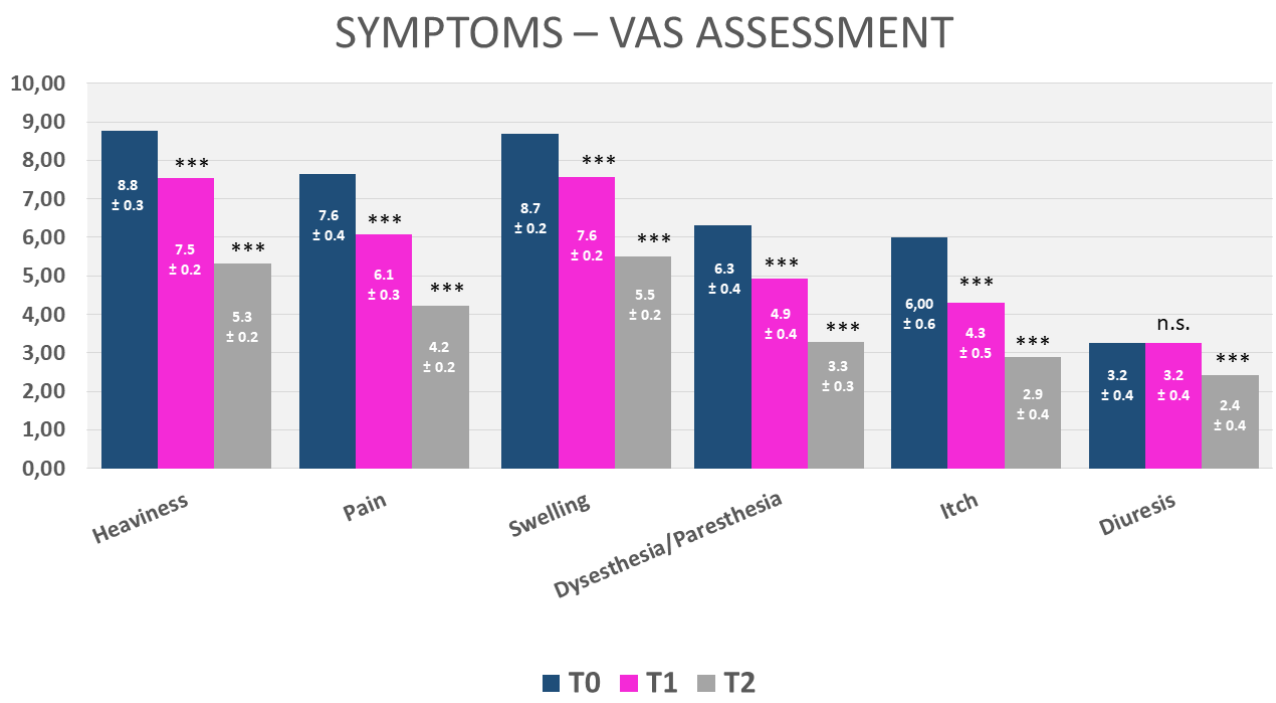

*Figure 1 - Symptoms at T0, T1 and T2. For each column the higher figure indicates the mean value and the lower figure indicates the standard error of the mean. The *** indicates a statistically significant difference with p value below 0.001 while n.s. points to a non-statistically significant result.*

Results

45 patients, 35 females and 10 males of mean age equal to 56.4 years (standard deviation, SD, +/- 11.5), were enrolled for the study. At T0 average BMI was 26.5 (SD +/- 3.2) and the distribution of C (highest value between the two limbs) of CEAP was as follows: 5 in C2, 31 in C3, 9 in C4. No specific adverse event was referred by the patients and none of them discontinued the intake of the nutraceutical. BMI showed no relevant variation at the end of the protocol. VAS assessment of the symptoms at one month (T1) and at two months follow-up (T2) showed an overall statistically significant improvement for all the investigated items (see Table I). Of interest, all the pre/post-therapy VAS figures showed a statistically significant ($p< 0.001$) decrease when comparing T2 figures with T0 ones; mean heaviness, pain, swelling sensation, paresthesias/dysesthesias and itching values at T0 and T2 were 8.8/5.3, 7.6/4.2, 8.7/5.5, 6.3/3.3 and 6.0/2.9 respectively. Diuresis improved from 3.2 to 2.4 ($p< 0.001$). Figure 1 summarises the outcomes at T0, T1 and T2, with the relative statistical significance.

Lower leg volumetry showed no statistically significant variation (3040 cc and 3060 cc at T0 and T2 respectively), though ankle circumference decreased of 2 mm in the average.

The algorithm-based analysis of SF12 questionnaire before and after treatment with Maqui 500®, showed an improvement of the items related to the mental component, from 23.2 (T0) to 37.0 (T2), which was statistically significant ($p<0.0001$). Conversely, the physical component did not show any relevant variation. In figure 2 a graphical representation of these outcomes is presented.

Blood assessment of CRP at T2 showed a decrease in the vast majority of the patients, though the variation was mild, from 2.8 to 2.6, which anyway resulted in a statistically significant change ($p<0.0001$) (see figure 3).

Table I summarises the main outcomes of the investigated parameters and all the relative statistical calculations.

Discussion

Scientific literature documented that maqui berry-derived nutraceuticals may improve a few biomarkers of cardiovascular diseases, inflammation and oxidative stress. Polyphenols and namely anthocyanins may have a role in CVD management[10-12, 15-22]. The high delphinidin content and antioxidant power of maqui[13,14] may combat the venous disease-related free radical excess and inflammation.

In fact, most effects of polyphenols seem to derive from a xenobiotic action on human cells[23];

more specifically they are considered hormetins[24], i.e. stressors which are able to stimulate a beneficial reaction through hormesis phenomenon[24, 25]; hormesis seems to play a significant role in chronic degenerative diseases and aging[24-26]. One of the most pertinent pathways in phlebology is represented by the activation of the nuclear related factor 2 (NrF2) transcription factor, with consequent mitochondrial antioxidant action and with free-radical quenching and anti- inflammatory repercussions.

Lastly polyphenols, such as the ones contained in maqui berry, are considered also valid prebiotics[27], which may positively impact microbiome; gut microbic flora seems to interact in multiple ways with the lymphatic system and edema ultimately[27,28].

The present preliminary cohort study aimed to assess the short-term efficacy and safety of the administration of a maqui-based nutraceutical in patients with CVD. Actually, a statistically significant improvement of the CVD symptoms at both follow-up controls was demonstrated in this cohort of patients, which was not the case for the edema-related findings.

A strict relationship between the autonomous nervous system and the vascular system was clearly shown through a few studies[29]; assessment of heart rate variability (HRV) represents the most reliable way to investigate parasympathetic and sympathetic activities and their consequent actions on cardiovascular system and general health[29,30].

In a recent publication[31] a direct action of Maqui 500® on parasympathetic and sympathetic systems was proven through HRV assessment[31]. This finding may partially explain the overall improvement of mental state after maqui intake, which is coherent with similar findings of other studies[20] where polyphenol supplementation proved to beneficially interfere with a few psychologic and neural patterns[32].

Our results are influenced by a great variability of the examined limbs, with a resulting high standard deviation, for example as to the pre-post-treatment volumetry.

Of interest, the (limited) reduction of CRP in our cohort of patients confirms a previously documented anti-inflammatory action of maqui and of polyphenols[33]. Recently, also a dose- dependent anti-nociceptive effect of maqui was documented in animals[34]: if proven in humans, this could contribute to explain the symptom amelioration in our patients.

Finally, an anti-platelet activity of maqui has been proven in a series of articles and in a recent review[35], where the inhibition of a few pathways typical of platelet aggregation has been highlighted. As blood coagulation/ aggregation imbalances invariably contribute to CVD evolution, this regulatory activity could represent an additional beneficial effect of this anthocyanin-rich berry.

One limitation of the study was the absence of a blood assessment of the oxidative stress, due to the impossibility to perform this exam in our setting; similarly, patients with more advanced CEAP stages (C5, C6) were excluded, which may have conditioned the final outcomes of our study. Furthermore, the absence of a control group may have limited the reliability of patients' reported outcomes. Theoretically, a longer duration/higher dose supplementation could have resulted in a more relevant improvement of the investigated parameters.

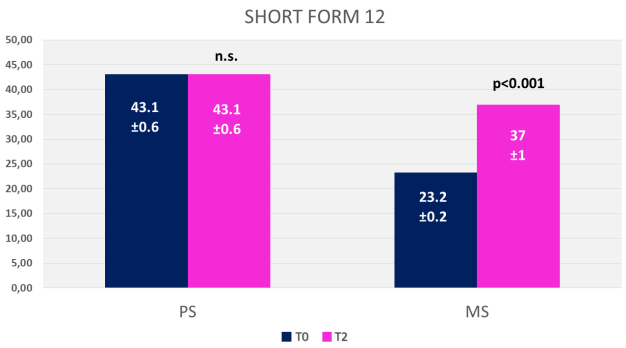

Figure 2 - Short-Form 12 (SF12) Questionnaire: Physical and Mental score before (T0) and 2 months after the nutraceutical intake (T2). For each column the higher figure indicates the mean value and the lower figure indicate the standard error of the mean. The ordinate (Y) axis indicates the SF12 score.

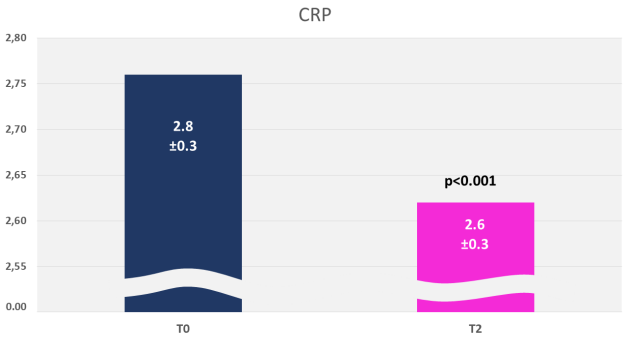

Figure 3 - C-Reactive Protein (CRP) figures before (T0) and 2 months after the nutraceutical intake (T2). For each column the higher figure indicates the mean value and the lower figure indicates the standard error of the mean. The ordinate (Y) axis indicates the mg/dl measure.

Conclusions

Venoactive compounds may play a role in the management of several venous diseases, with regards both to symptomatology and to a few basic pathophysiologic mechanisms.

Notwithstanding the limitations of this preliminary protocol, this prospective cohort study seems to indicate that the investigated nutraceutical may achieve overall beneficial effects, especially on symptoms of CVD patients. The achieved short-term improvement of the inflammation biomarkers and of mental state, in combination with a good safety profile, concur to favour the execution of future trials regarding this nutraceutical supplementation.

More comprehensive studies are necessary before drawing any sound conclusions on this supplement-based approach to CVD, which seems to possibly target a few of its basic pathologic mechanisms, such as inflammation, oxidative stress and vein/capillary wall protection.

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